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SPECIAL ISSUE

SYNTHESES OF *C*-GLYCOSYL COMPOUNDS

A Collection of Invited Papers

The invitation of papers for this volume of *Carbohydrate Research* was coordinated by Professor P. Sinaÿ (École Normale Supérieure, Paris) and the Editors gratefully acknowledge his cooperation.

FOREWORD

SYNTHESES OF *C*-GLYCOSYL COMPOUNDS

The biological importance of *C*-nucleosides was primarily responsible for the search for synthetic methods which allowed carbon–carbon bond formation at the anomeric position of carbohydrates. This is clearly reflected by a review written in 1976 by S. Hanessian and A. G. Pernet in Advances in Carbohydrate Chemistry and Biochemistry.

In the last decade, and especially in the past few years, the direct formation of C–C bonds at the anomeric center of carbohydrates has attracted considerable attention. One basic reason for such efforts is the presence of 2,5-dialkylated oxolane (*C*-glycofuranosyl compounds) and 2,6-dialkylated oxane units (*C*-glycopyranosyl compounds) in a wide variety of complex natural products; the marine natural compound palytoxin is a spectacular example. Furthermore, synthetic *C*-glycosyl compounds represent interesting starting chiral synthons, suitable for the synthesis of complex molecules, as they contain a larger number of chiral centers and functional groups. Monosaccharides have frequently been used as natural sources of stereocenters for the total synthesis of optically-active, "chirally rich", natural compounds. In most cases, appropriate manipulation of various cyclic pentoses and hexoses ultimately resulted in short segments that are the starting material for "off-template" chemistry. All things considered, the anomeric center of a monosaccharide is thus an off-template site which is only used to lock the molecule in the most desirable heterocyclic form, thus allowing the principles of conformational parameters to operate for the control of the endocyclic chiral transformations.

One attractive way of synthesizing a higher-carbon sugar possessing multiple chiral centers is indeed to take advantage of the anomeric stereoselection—a general phenomenon which is valid for C–C bond formation. Reactions of carbon nucleophiles at the electrophilic anomeric center of carbohydrates are by far the most exploited routes to *C*-glycosyl syntheses. They involve mainly the attack of various *C*-nucleophiles at the anomeric center of glycosyl halides, *O*-glycosylimidates, lactones, glycosides, thioglycosides, or glycals. Several selected examples of this traditional approach will be found in this issue. They include both Friedel–Crafts-type reactions or Michael additions. The stereoselective formation of *C*-glycosyl compounds *via* addition of an anomeric radical to alkenes has proved to be a versatile and mild procedure. It is an interesting case of manipulation of carbohydrate radicals, a field that is currently attracting wide interest and will probably

grow rapidly as radical chemistry is particularly suitable for polyfunctional, complex molecules.

A new, flexible concept is based on the "Umpolung" of the chemical reactivity at the anomeric center. Thus, efficient and stereocontrolled introductions of carbon appendages have been described recently; they use either stabilized anomeric carbanions derived from anomeric phosphonium salts, nitro and phenylsulfonyl derivatives, pentacarbonylglycosylmanganese complexes, or 2-deoxy-D-gluco-pyranosyllithium reagents. One of the reasons for the rapid development of this field of research is the current interest of leading synthetic organic chemists in *C*-glycosyl compounds. Such a trend should undoubtedly be beneficial to the specialized field of carbohydrate chemistry.

A recent consequence of this flourishing carbohydrate chemistry area is the availability of *C*-disaccharides, which are disaccharides in which a methylene group takes the place of the interunit oxygen atom. *C*-Linked oligosaccharides are now highly in demand for studies of sugar metabolism and as enzyme inhibitors. These compounds also provide a unique opportunity to estimate the contribution of the *exo*-anomeric effect on the conformational preference of an oligosaccharide. It is hoped that this special issue dedicated to a rapidly growing field is timely and will stimulate further developments.

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STEREOSELECTIVITY IN THE ELECTROPHILE-MEDIATED CYCLIZATION OF 2,3,5-TRI-*O*-BENZYL-1,2-DIDEOXY-D-*arabino*-HEX-1-ENITOL. A STEREOCONTROLLED SYNTHESIS OF 1-AMINO-2,5-ANHYDRO-3,4,6-TRI-*O*-BENZYL-1-DEOXY-D-GLUCITOL

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ABSTRACT

Cyclization of 2,3,5-tri-*O*-benzyl-1,2-dideoxy-D-*arabino*-hex-1-enitol (**2**) with mercuric acetate, mercuric trifluoroacetate, iodine, and *N*-bromosuccinimide gave preponderantly the *allo* isomer of the *C*-arabinofuranosyl structure. 1-Amino-2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-D-glucitol, which is a key intermediate in the synthesis of 3-(β-D-arabinofuranosyl)pyrazole[4,3-*d*]pyrimidine-5,7-dione (β-D-*arabino* epimer of oxoformycin B), was stereoselectively prepared in 48% overall yield from **2** in three steps. The stereochemical outcome of the cyclizations is also discussed.

INTRODUCTION

In 1974, Acton *et al.*[1] synthesized the α- and β-D-*arabino* (**6**) epimers of the naturally occurring *C*-nucleoside oxoformycin B. We wish to report a stereoselective synthesis of Acton's key intermediate, 1-amino-2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-D-glucitol (**5**), in three steps (from **2**) *with excellent control* of the anomeric center to give preponderantly the β-D-*arabino* epimer. During this study, it was observed that electrophile-mediated cyclizations of 2,3,5-tri-*O*-benzyl-1,2-dideoxy-D-*arabino*-hex-1-enitol[2] (**2**) were highly stereoselective, with a strong preference for formation of *C*-arabinofuranosyl derivatives which have the *cis* arrangements of substituents at C-2 and C-3.

RESULTS AND DISCUSSION

The synthesis of **5** was accomplished by reaction of methylidenetriphenylphosporane (2.0 equiv. from the phosphonium bromide and butyllithium)[2,3] with 2,3,5-tri-*O*-benzyl-D-arabinose[4] (**1**) in oxolane to give hydroxyolefin **2** in 94% yield. Cyclization with iodine[3–6] gave a mixture of *allo* and *altro* in 79% yield, which was

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TABLE I

ELECTROPHILE-MEDIATED CYCLIZATIONS OF 2,3,5-TRI-*O*-BENZYL-1,2-DIDEOXY-D-

Electrophile	*Ref.*	*Reaction conditions*
I_2	2, 3	10 eq. sat'd $NaHCO_3$, 5 eq. I_2–oxolane; 24°, 4 h
Br_2	9	*N*-Bromosuccinimide (1.5 eq.)–$HCONMe_2$; 24°, 2 h
$Hg(OAc)_2$	10	(a) $Hg(OAc)_2$ (1.5 eq.)–oxolane; 24°, 3 h (b) sat'd KCl
$Hg(OCOCF_3)_2$	11	(a) $Hg(OCOCF_3)_2$ (1.5 eq.)–oxolane; 24°, 3 h (b) sat'd KCl
PheSeCl	12	PheSeCl (1.5 eq.)–oxolane; −78→24°, 8 h
PheSeCl	12, 14	PheSeCl (1.5 eq.)–oxolane–K_2CO_3 (2.0 eq.)
3-Chloro-peroxybenzoic acid	8	3-Chloroperoxybenzoic acid (1.2 eq.)–$(CH_2)Cl_2$;16, 18 h, reflux

[a]^{13}C-Chemical shifts are referenced to the signal of $CDCl_3$ at δ 77.27. All ^{13}C-s numbers in parentheses are those reported by Reitz *et al.*[8]. [b]The *allo*-to-*altro* min)[11] of *crude* cyclization products and analysis of the *crude* methyl compoun methyl doublets gave the *allo*-to-*altro ratios*. [c]The *allo*-to-*altro* ratio was dete min)] of the crude organomercurial and ^{1}H-n.m.r. (250 MHz) analysis of a solu recovery of starting material resulted. [e]The *allo*-to-*altro* ratio was determined b

XY-D-*arabino*-HEX-1-ENITOL (**2**)

	Yield (%)		allo *(β)-to-* altro *(α) ratio*	*^{13}C-N.m.r. (δ)*[a]	
	Crude	*Pure*		allo	altro
	85	79	82:18[b]	0.68	7.14
e_2;	85	75	84:16[b](89:11)	28.26(28.20)	32.37(32.30)
	100	87	89:11[c,d](87:13)	28.33	35.45
3 h	83	63	89:11[c,d]	28.33	35.45
n	100	46	40:60[b]	25.47	29.98
q.)	100	48	85:15[b]	25.47	29.98
		33	50:50[e](55:45)	61.71	62.73

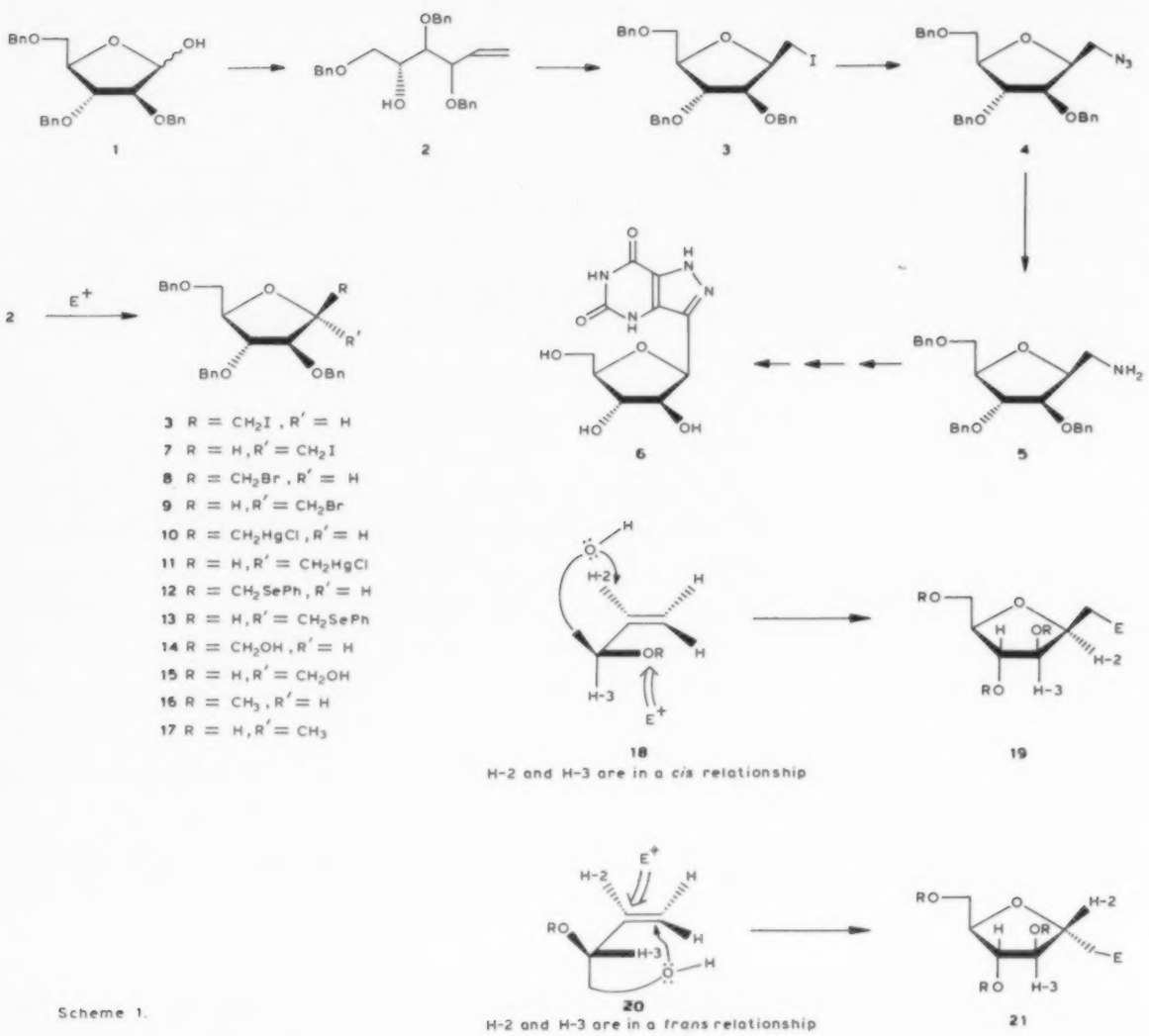
^{13}C-spectra were taken for solutions in $CDCl_3$. $J_{2,3}$ in compound **3** = 3.6 Hz. The *altro* ratio was determined by reduction (azoisobutyronitrile–Bu_3SnH–C_6H_6; 45 pound by ^{1}H-n.m.r. (250 MHz) in C_6D_6. Integration of the two sets of anomeric determined by reduction [$NaBH_4$ (excess)-$BnEt_3NCl$(10 eq.)–10% NaOH; 0°, 2 solution in C_6D_6. [d]$HgBr_2$ or $HgCl_2$[11] did not effect cyclization. Only quantitative ed by ^{1}H-n.m.r. (250 MHz) integration of the two OH triplets.

highly enriched in the *allo* anomer (Table I). Flash column chromatography gave the anomerically pure *allo* isomer (**3**). Reaction of **3** with 1,1,3,3 tetramethylguanidinium azide in *N,N*-dimethylmethanamide at 80° for 1 h (71%), followed by lithium aluminum hydride reduction at 0° in diethyl ether, gave the desired amine[7] **5** (90%). This short, stereocontrolled synthesis of **5** took advantage of a highly stereoselective, electrophile-mediated cyclization to control the stereochemistry at the anomeric center.

The stereoselectivity shown by the cyclization of **2** with iodine prompted us to study this reaction further with a series of electrophiles. Though the method to quantify *allo*-to-*altro* ratios in the cyclized products differs from that used by Reitz *et al.*[8], these results are in excellent agreement with their report[9–14] (Table I). The steric structure of the cyclization products was determined by the relative positions and intensities in the ^{13}C-n.m.r. of the C-1 signals[8]. The 1:1 mixture of **14** and **15** was converted into the iodo compounds by the procedure of Ho and Davies[15] (triphenylphosphine, diethyl azodicarboxylate, zinc iodide, 30%). Two ^{13}C resonances were observed for the iodomethyl carbon atoms at δ 7.14 and 0.68. The ^{13}C-n.m.r. spectrum of the crude reaction mixture from the cyclization of **2** with iodine showed a major resonance for the iodomethyl carbon atom at δ 0.68 and another smaller resonance (*ca.* one-fifth the height) at δ 7.14. Ohrui *et al.*[16] have shown that for furanoses the ^{13}C-chemical shift of a carbon atom bonded to the anomeric center in the 2,3-*cis* isomer [*allo* (β) isomer in this case] is 3–4 p.p.m. *upfield* of that for the corresponding 2,3-*trans* isomer [*altro* (α) isomer in this case].

In addition, upon decoupling of H-1A,B in **3**, the H-2 signal collapsed to a *doublet* with a $J_{2,3}$ value of 3.6 Hz. Similarly, decoupling of the anomeric methyl group of its reduction product gave a $J_{2,3}$ value of 3.7 Hz. These values are indicative of a *cis* relationship between H-2 and H-3. This, in conjunction with the relative positions of the iodomethyl carbon atom signals in the ^{13}C-n.m.r. spectrum allowed the assignment of the *allo* (β) structure to the major product of the cyclization with iodine. The configurations of the other cyclization products were assigned accordingly. With the exception of the selenium-mediated cyclization, this observed stereoselectivity was in accord with the selectivity reported by other investigators[8,10,13,17–19].

Unlike the cyclization of 6-*O*-benzyl-1,2-dideoxy-3,4-*O*-isopropylidene-D-*ribo*-hex-1-enitol[3], the stereochemical outcome of the cyclization in alkene **2** is dependent upon the electrophile. Iodine, bromine, mercury(II) acetate and mercury(II) trifloroacetate, all showed a stereoselective preference for *C*-arabinofuranosyl derivatives that have a *cis* arrangement of H-2 and H-3 (*allo* isomer). 3-Chloroperbenzoic acid showed no selectivity and with phenylselenyl chloride the *altro* isomer was slightly preferred. Although the reversal of stereochemistry shown by the selenium-induced cyclization is not clear, it may be due to an acid-catalyzed equilibration of the epimers, since the *allo* isomer is the major product in the presence of base*. Lancelin *et al.*[21] have reported a selenium-induced cyclization in which the stereochemical result is consistent with these


1
2
3
4
5
6
3 R = CH2I, R' = H
7 R = H, R' = CH2I
8 R = CH2Br, R' = H
9 R = H, R' = CH2Br
10 R = CH2HgCl, R' = H
11 R = H, R' = CH2HgCl
12 R = CH2SePh, R' = H
13 R = H, R' = CH2SePh
14 R = CH2OH, R' = H
15 R = H, R' = CH2OH
16 R = CH3, R' = H
17 R = H, R' = CH3
18
H-2 and H-3 are in a cis relationship
19
20
H-2 and H-3 are in a trans relationship
21

Scheme 1.

observations. For this kinetically controlled reaction[8], it appears as though the allylic ether oxygen atom is again controlling the stereochemical outcome of the cyclization[3]. There seems to be a preference to cyclize through a "transition state" in which the OR residue (Scheme 1) is in the plane of the prochiral olefin. In this conformation, the internal nucleophile is positioned to trap from above, as depicted in Scheme 1. Electrophile approach from the least hindered side (below, **18**), followed by trapping by the internal nucleophile leads to H-2 and H-3 in a *cis* relationship to one another (*i.e.*, the *β-arabino* epimer). Cyclization through conformation **20**, in which the hydrogen atom eclipses the prochiral olefin, leads to the *α-arabino* product (*altro* isomer).

*The modest yield of products (46%) suggests possible competing-side reactions. For example, there may be decomposition of the products at differing rates under the experimental conditions which would effect the final *allo* to *altro* ratio. The stereochemical outcome of the selenium mediated cyclization of **2** is dependent on the reaction conditions. Use of camphorsulfonic acid and N-(phenylseleno)phthalimide in refluxing benzene gave a 2:1 *allo*-to-*altro* ratio[20].

In the absence of any steric bias, the preference for reactions of this type to cyclize *via* a "reactive conformer" resembling **18** may be very general. For example, the stereoselectivity observed in iodolactonizations of allylic alcohols[22] and iodoetherifications[23,24] to form functionalized oxolanes can be rationalized accordingly. This "working model" is useful for predicting *a priori* the stereochemical outcome for these cyclizations in which there is a preference for a *cis* relationship between the substituents at C-2 and C-3 in the newly formed oxolane ring.

EXPERIMENTAL

General methods. — Melting points were determined in open capillary tubes with a Thomas–Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter in an unthermostatted 10-cm glass cell at the sodium D line. I.r. spectra were obtained with a Perkin–Elmer 283 spectrophotometer for dilute solutions in CCl_4, neat films, or KBr disks. Medium-resolution mass spectra were obtained with a Finnigan 9610 g.l.c.–c.i. mass spectrometer with a Nova 3 data system operating at an ionization potential of 70 or 100 eV. Chemical-ionization mass spectra were obtained by use of 2-methylpropane as the reactant gas. Peaks greater than ~10% relative intensity are generally reported. ^{1}H-N.m.r. spectra were recorded at 250 MHz (Bruker WM-250) with the solvent(s) noted. Chemical shifts (δ) are reported downfield from the internal Me_4Si signal (~0.5% for Fourier transform) at δ 0.00 (Abq, ab quartet; br, broad; d, doublet; m, multiplet; q, quartet; s, singlet; and t, triplet). Apparent coupling-constants (J) are reported in hertz (Hz). Because of the data digitization with the F.t. instrument, J values are ±0.40 Hz maximum, but normally are accurate to ±0.20 Hz. ^{13}C-N.m.r. data were obtained with a Bruker WM-250 spectrometer. Silica gel 60 (230–400 mesh) was used for flash column chromatography. T.l.c. was performed on Merck Silica gel 60 F-254 (0.25 mm, precoated on glass). Solvents used for extraction and chromatography were nanograde quality or distilled. Oxolane and ether were distilled from sodium benzophenone anion prior to use. Dichloromethane was distilled from CaH_2 prior to use. *N,N*-Dimethylmethanamide was predried over BaO, and then distilled under diminished pressure from CaH_2 in the dark and stored over 4A sieves. Other reagents were used as supplied or purified as noted. Butyllithium in hexane (Alfa) was titrated at 24° in oxolane with (2,5-dimethoxyphenyl)methanol. All reactions were carried out in oven- or flame-dried glassware under Ar with magnetic stirring, unless noted otherwise. Solutions and liquids were delivered by syringe or cannula through rubber septa or by pressure-equalizing dropping funnels where appropriate. Elemental analyses were performed by Robertson Laboratory, Florham Park, NJ.

*2,3,5-Tri-*O*-benzyl-1,2-dideoxy-*D-arabino-*hex-1-enitol* (**2**). — To a stirred solution of methyltriphenylphosphonium bromide (2.80 g, 7.92 mmol; Aldrich, predried at 140°, 18 h) in dry oxolane (25 mL) at 25° under Ar was added dropwise

2.4M butyllithium in hexane (2.97 mL, 7.13 mmol) over 8 min. A color change from yellow to red occurred. The mixture was stirred for 15 min at 24° and a solution of 2,3,5-tri-*O*-benzyl-D-arabinose[4] (**1**) (1.5 g, 3.57 mmol) in oxolane (10 mL) was added over 3 min. Solids began to form in the cream-colored suspension. The mixture was stirred for 18 h at 24° under Ar and the reaction quenched by the addition of wet ether (100 mL). The mixture was extracted several times with ether, and the combined organic layers were washed with saturated aqueous NaCl (35 mL), and dried (K_2CO_3). Removal of solvent under reduced pressure and flash-column chromatography of the residue on silica (60 g) with 3:1:1 petroleum ether-(35–60°)–ether–dichloromethane afforded **2** (1.40 g, 94%), $[\alpha]_D^{26}$ +4.6° (*c* 1.15, chloroform), R_F 0.30 (3:1:1 petroleum ether–ether–dichloromethane); ν_{max}^{film} 3540–3460 (br, OH), 3100, 3080, 3040 (alkene, arom.), 2920, 2880 (CH_2,CH), 1500, 1460 (arom. ring), 1400, 1350, 1225, 1080, 930 (vinyl), 740, and 700 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 7.35–7.24 (m, 15 H, Ph), 5.97 (ddd, 1 H, $J_{1,2(trans)}$ 16.5, $J_{1,2(cis)}$ 11.3, $J_{2,3}$ 7.5 Hz, H-2, X part of ABX), 5.33 (m, 2 H, H_2-1), 4.60 (ABq, 2 H, $\Delta\nu_{AB}$ 18.4, J_{AB} 11.5 Hz, OCH_2Ph), 4.52 (s, 2 H, OCH_2Ph), 4.51 (ABq, 2 H, $\Delta\nu_{AB}$ 69.5, J_{AB} 12.0 Hz, OCH_2Ph), 4.09 (dd, 1 H, $J_{2,3}$ 7.5, $J_{3,4}$ 4.0 Hz, H-3), 4.03 (m, 1 H, H-5), 3.64 (dd, 1 H, $J_{3,4}$ 4.0, $J_{4,5}$ 7.0 Hz, H-4), 3.61 (d, 2 H, $J_{5,6}$ 4.0 Hz, H_2-6), and 2.84 (d, 1 H, $J_{5,OH}$ 5.0 Hz, OH); ^{13}C-n.m.r. ($CDCl_3$): δ 138.47, 138.38, 138.17 (s, C quat., O*C*H_2Ph), 135.40 (d, C-2), 128.61–127.91 (m, OCH$_2$*C*$_6$H$_5$), 119.31 (t, C-1), 80.89 (d, C-3), 80.48 (d, C-4), 74.35 (t, O*C*H_2Ph), 73.62 (t, C-6), 71.22 (t, O*C*H_2Ph), 70.95 (d, C-5), and 70.65 (t, O*C*H_2Ph); m.s. (c.i.): *m/z* 419 (MH^+), 219, 181, 129, 107, and 91.

Anal. Calc. for $C_{27}H_{30}O_4$: C, 77.48; H, 7.22. Found: C, 77.42; H, 7.37.

*2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-iodo-*D*-allitol* (**3**). — Alkene **2** (3.34 g, 7.99 mmol) was cyclized with iodine as described previously[3,6]. Work-up as usual[3], followed by flash-column chromatography on silica (175 g) in 9:1:1 petroleum ether (35–60°)–ether–dichloromethane yielded the anomerically pure iodo compound **3** (3.43 g, 79%), $[\alpha]_D^{28}$ +41.1° (*c* 1.78, chloroform), R_F 0.30 (9:1:1 petroleum ether–ether–dichloromethane); ν_{max}^{film} 3080, 3060, 3020 (alkene, arom.), 2910, 2860, (CH_2, CH), 1500, 1450 (arom. ring), 1370, 1210, 1100, 740, and 697 cm^{-1} (monosubst. arom.); ^{1}H-n.m.r. ($CDCl_3$): δ 7.39–7.24 (m, 15 H, Ph), 4.62–4.43 (m, 6 H, 3 OCH_2Ph, no ABq's could be determined), 4.35 (ddd, 1 H, $J_{2,3}$ 3.6, $J_{1,2}$ 6.0, $J_{1,2}$ 5.5 Hz, H-2, collapsed to d upon irradiating H-1A,B and a dd upon irradiating H-3), 4.24 (dt, 1 H, $J_{4,5}$ 2.0, $J_{5,6}$ 6.0 Hz, H-5), 4.05 (br. d, 1 H, $J_{2,3}$ 3.6 Hz, H-3), 3.96 (br. d, 1 H, $J_{4,5}$ 2.0 Hz, H-4), 3.60 (dd, 1 H, $J_{6A,B}$ 10, $J_{6,5}$ 6.0 Hz, H-6A or 6B), 3.49 (dd, 1 H, $J_{6A,B}$ 10, $J_{6,5}$ 7.0 Hz, H-6A or 6B), and 3.34 (m, 2 H, H_2-1); ^{13}C-n.m.r. ($CDCl_3$): δ 138.28, 137.85, 137.72 (s, C quat., O*C*H_2Ph), 128.64–127.79 (m, OCH$_2$*C*$_6$H$_5$), 83.97 (d, C-2), 83.33 (d, C-5), 82.74 (d, C-3), 82.18 (d, C-4), 73.48, 72.27, 71.62 (t, O*C*H_2Ph), 70.65 (t, C-6), and 0.68 (t, C-1); m.s. (c.i.): *m/z* 545 (MH^+), 453, 181, 107, and 91.

Anal. Calc. for $C_{27}H_{29}IO_4$: C, 59.57; H, 5.37; I, 23.31. Found: C, 59.40; H, 5.48; I, 23.04.

Compound **3** could also be prepared by the addition of solid iodine (until the red color persisted) to an oxolane solution of the corresponding organomercurial compound[3]. Work-up as usual, followed by flash chromatography, gave a product identical in all respects with the one obtained by cyclization with iodine.

*2,5-Anhydro-1-azido-3,4,6-tri-*O*-benzyl-1-deoxy-*D*-allitol* (**4**). — Compound **3** (284.3 mg, 0.52 mmol) was dissolved in *N,N*-dimethylmethanamide (5 mL) and solid 1,1,3,3-tetramethylguanidinium azide (Alfa) (165.0 mg, 1.04 mmol) was added quickly. The mixture was heated to 80° and stirred at 80° for 20 min. The color changed from clear to golden upon heating. The starting material was completely consumed at this time as determined by t.l.c. (3:1:1 petroleum ether–ether–dichloromethane). The mixture was heated an additional 20 min, cooled, and evaporated under vacuum (50°, 4 kPa) to leave a crude yellow oil. Flash chromatography on silica (10 g) in 9:1:1 petroleum ether–ether–dichloromethane gave pure azide (**4**) (170.4 mg, 71%), $[\alpha]_D^{26}$ +7.7° (*c* 0.78, chloroform), R_F 0.30 (9:1:1 petroleum ether–ether–dichloromethane); ν_{max}^{film} 3100, 3075, 3040 (alkene arom.), 2930, 2870 (CH_2, CH), 2100 (N_3), 1500, 1455 (arom. ring), 1370, 1160–1050 (br. OR), 740 and 695 cm^{-1} (monosubst. arom.); ^{1}H-n.m.r. ($CDCl_3$): δ 7.40–7.22 (m, 15 H, Ph), 4.7–4.39 (m, 6 H, 3 OCH_2Ph, no ABq's could be deermined), 4.23–4.15 (m, 2 H, H-2,5), 4.0 (m, 2 H, H-3,4), and 3.70–3.40 (m, 4 H, H-1, H-6); ^{13}C-n.m.r. ($CDCl_3$): δ 138.37, 137.91, 137.68 (s, C quat., OCH_2Ph), 128.70–127.85 (m, $OCH_2C_6H_5$), 83.35 (d), 83.14 (d), 82.94 (d), 79.74 (d), 73.56 (t), 71.81 (t), 70.53 (t), and 50.27 (t, C-1); m.s. (c.i.): *m/z* 460 (MH^+), 432 (MH^+ −28), 205, 181, 120, 107, and 91.

Anal. Calc. for $C_{27}H_{29}N_3O_4$: C, 70.57; H, 6.36; N, 9.14. Found: C, 70.44; H, 6.43; N, 9.01.

*1-Amino-2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-*D*-allitol*[7] (**5**). — Compound **4** (86.4 mg, 0.190 mmol) was dissolved in dry diethyl ether (5 mL). The reaction vessel was cooled in an ice–water bath to 0–5°. Excess $LiAlH_4$ (36.0 mg, 0.95 mmol) was added and the reaction stirred at 0–5° for 30 min. The mixture was diluted to 15 mL with diethyl ether and solid $Na_2SO_4 \cdot 10\ H_2O$ was added in small portions at 0° until effervescence ceased. Water (1.0 mL) was then added cautiously to ensure that $LiAlH_4$ was fully quenched. The liquid was then decanted from the fine granular precipitate and evaporated to give 81.0 mg (100%) of a yellow oil. Flash-column chromatography on silica (3.5 g) with 10:0.5:0.25 chloroform–methanol–NH_4OH yielded the pure *allo* epimer **5** (73.6 mg, 90%), $[\alpha]_D^{23.5}$ +88.0° (*c* 2.09, chloroform), R_F 0.30 (10:0.5:0.25 chloroform.methanol–NH_4OH; stains red with ninhydrin spray followed by charring); ν_{max}^{film} 3380 (NH_2), 3320 (NH_2), 3100, 3080, 3040 (alkene arom.), 2920, 2880 (CH, CH_2), 1500, 1460 (arom. ring), 1370, 1220, 1150–1080 (br, OR), 740 and 698 cm^{-1} (monosubst. arom.); ^{1}H-n.m.r. ($CDCl_3$): δ 7.34–7.20 (m, 15 H, Ph), 4.58–4.30 (m, 6 H, 3 OCH_2Ph, but no ABq's could be determined), 4.06 (m, 1 H, H-5), 3.93 (m, 3 H, H-2,3,4), 3.57 (dABq, 2 H, $\Delta\nu_{AB}$ 16.2, J_{AB} 10.0, $J_{5,6}$ 6.0 Hz, H-6A,B), and 2.94 (m, 2 H, H-1); ^{13}C-n.m.r. ($CDCl_3$): δ 138.28, 137.97, 137.90 (s, C quat., OCH_2Ph), 128.55–127.75 (m,

$OCH_2C_6H_5$), 83.83 (d), 83.40 (d), 82.39 (d), 73.42 (t), 71.68 (t), 71.60 (t), 70.66 (t), and 41.56 (t, C-1); m.s. (c.i.): *m/z* 434 (MH^+), 205, 181, 107, and 91.

Anal. Calc. for $C_{27}H_{31}NO_4 \cdot 0.5\ H_2O$: C, 73.27; H, 7.29; N, 3.16. Found: C, 73.43; H, 6.99; N, 3.10.

*2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-bromo-1-deoxy-*D*-allitol* (**8**) *and* -D-*altritol*[9] (**9**). — An *N,N*-dimethylmethanamide solution (3.75 mL) of *N*-bromosuccinimide (75.0 mg, 0.45 mmol) was added at 24° to a stirred solution of alkene **2** (150 mg, 0.36 mmol) in *N,N*-dimethylmethanamide (0.75 mL). The mixture was stirred for 2 h at 24° at which time all starting material had been consumed (t.l.c. assay). The mixture was diluted with ethyl acetate (25 mL) and washed successively with saturated $NaHCO_3$ (10 mL), water, and saturated NaCl. The organic layer was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a clear oil (152 mg, 85%). The crude product could be purified by flash chromatography in 9:1:1 petroleum ether-(35–60°)–ether–dichloromethane leading to >95% enrichment in the *allo* epimer (**8**) (75% purified); $[\alpha]_D^{23}$ +32.3° (*c* 2.52, chloroform), R_F 0.30 (9:1:1 petroleum ether–ether–dichloromethane); ν_{max}^{film} 3100, 3075, 3040 (alkene, arom.), 2920, 2870 (CH_2,CH), 1500, 1450 (arom. ring), 1100, 740, and 697 cm^{-1} (monosubst. arom.); ^{1}H-n.m.r. ($CDCl_3$): δ 7.37–7.25 (m, 15 H, Ph), 4.61–4.47 (m, 6 H, 3 OCH_2Ph, no ABq's could be determined), 4.32 (m, 1 H, H-2), 4.21 (dt, 1 H, $J_{4,5}$ 2.0, $J_{5,6}$ 6.0 Hz, H-5), 4.03 (br. d, 1 H, $J_{2,3}$ 3.6 Hz, H-3), 3.96 (br. d, 1 H, $J_{4,5}$ 2.0 Hz, H-4), and 3.61–3.47 (m, 4 H, H_2-6, H_2-1); ^{13}C-n.m.r. ($CDCl_3$): δ 138.20, 137.72, 137.64 (s, C quat., OCH_2Ph), 128.56–127.79 (m, $OCH_2C_6H_5$), 83.65 (d, C-2), 83.17 (d, C-5), 82.21 (d, C-3), 81.47 (d, C-4), 73.39, 72.06, 71.53 (t, OCH_2Ph), 70.42 (t, C-6), and 28.26 (t, C-1); m.s. (c.i.): *m/z* 499 (MH^+, ^{81}Br), 497 (MH^+, ^{79}Br), 271, 181, and 91.

Anal. Calc. for $C_{27}H_{29}BrO_4$: C, 65.32; H, 5.89; Br, 15.89. Found: C, 65.03; H, 6.13; Br. 15.73.

*2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-mercuriochloro-*D*-allitol* (**10**). — The general cyclization procedure and work-up described by Nicotra *et al.*[10] was used. Mercuric acetate and mercuric trifluoroacetate gave cyclized product in 100 and 83% crude yields, respectively. HgCl and HgBr[11] did not effect cyclization. The compound could be purified by flash-column chromatography in 3:1:1 petroleum ether-(35–60°)–ether–dichloromethane to yield the anomerically pure *allo* isomer **10**, $[\alpha]_D^{28}$ −20.3° (*c* 1.76, chloroform), R_F 0.27 (3:1:1 petroleum ether–ether–dichloromethane); ν_{max}^{film} 3090, 3075, 3040 (alkene, arom.), 2920, 2875 (CH_2, CH), 1610, 1590, 1500, 1460 (arom. ring), 1365, 1210, 1100–1040, 740 and 697 cm^{-1} (monosubst. arom.); ^{1}H-n.m.r. ($CDCl_3$): δ 7.36–7.24 (m, 15 H, Ph), 4.63–4.33 (m, 7 H, 3 OCH_2Ph and H-2, no ABq's could be determined), 4.11 (m, 1 H, H-5), 3.92 (d, 1 H, $J_{4,5}$ 2.70 Hz, H-4), 3.74 (d, 1 H, $J_{2,3}$ 3.5 Hz, H-3), 3.53 (dABq, 2 H, $\Delta\nu_{AB}$ 28.4, J_{AB} 9.8, $J_{5,6}$ 6.0 Hz, H-6A,B), 2.18 (dd, 1 H, $J_{1A\text{ or }1B,2}$ 5.6, $J_{1A,B}$ 12.5 Hz, H-1A or B), and 1.80 (dd, 1 H, $J_{1A\text{ or }1B,2}$ 2.8, $J_{1A,B}$ 12.5 Hz, H-1A or B); ^{13}C-n.m.r. ($CDCl_3$): δ 138.26, 137.79, 137.02 (s, C quat., OCH_2Ph), 128.73–127.91 (m, $OCH_2C_6H_5$), 83.92 (d, C-2), 83.44 (d, C-5), 83.20 (d, C-4), 79.27 (d, C-3), 73.61,

71.92, 71.75 (t, OCH_2Ph), 70.80 (t, C-6), and 28.37 (t, C-1); m.s. (c.i.): *m/z* 621 ($MH^+ - {}^{37}Cl$), 619 ($MH^+ - {}^{35}Cl$), 529, 181, 107, and 91.

Anal. Calc. for $C_{27}H_{29}ClHgO_4$: C, 49.62; H, 4.47. Found: C, 49.80; H, 4.60.

Typically, further manipulations of **10** were carried out on the crude organomercurial compound.

*2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-phenylseleno-*D*-allitol* (**12**) *and* -D-*altritol* (**13**). — Cyclization by the method of Nicolaou[3,12], followed by flash-column chromatography in 9:1:1 petroleum ether-(35–60°)–ether–dichloromethane, gave a 46% yield of a colorless oil. The product was an inseparable mixture of diastereomers (1.0:1.5 *allo*-to-*altro* ratio) as determined by ^{1}H- and ^{13}C-n.m.r. spectroscopy; $[\alpha]_D^{23}$ +7.5° (*c* 2.8, chloroform), R_F 0.20 (9:1:1 petroleum ether–ether–dichloromethane); ν_{max}^{film} 3100, 3070, 3040 (alkene, arom.), 2930, 2870 (CH_2, CH), 1585, 1500, 1455 (arom. ring), 1370, 1210, 1120–1050, 740, 695 cm^{-1} (monosubst. arom.); ^{1}H-n.m.r. ($CDCl_3$): δ 7.52–7.22 (m, 20 H, Ph), 4.60–4.44 (m, 6 H, 3 OCH_2Ph, no ABq's could be determined), 4.32–4.25 (m, 2 H, H-2,5), 4.13 (app. t, 1 H, $J_{3,4} \simeq J_{4,5}$ 2.5 Hz, H-4), 4.07 (br. d, 1 H, $J_{3,4}$ 2.5 Hz, H-3), and 3.64–3.51 (m, 4 H, H_2-1, H_2-6); ^{13}C-n.m.r. ($CDCl_3$): δ 29.98 (t, C-1 *altro*) and 25.47 (t, C-1 *allo*); m.s. (c.i.): *m/z* 575 (MH^+, ^{79}Se), 271, 181, and 91.

Anal. Calc. for $C_{33}H_{34}O_4Se$: C, 69.10; H, 5.97. Found: C, 69.34; H, 6.24.

*2,5-Anhydro-3,4,6-tri-*O*-benzyl-*D*-allitol* (**14**) *and* -D-*altritol*[8] (**15**). — Compound **1** (258.9 mg, 0.62 mmol) was dissolved in freshly distilled (from CaH_2) dichloroethane (6 mL). 3-Chloroperbenzoic acid (60 mg, 0.93 mmol) was added all at once. The mixture was refluxed for 19 h and cooled to 0°. The resulting solid was removed by filtration and the filtrate evaporated under reduced pressure. Crude ^{1}H-n.m.r. analysis showed ~15% of unreacted alkene present. Column chromatography in 1:1:1 petroleum ether–ether–dichloromethane gave a 1:1 mixture of *allo* (**14**) and *altro* (**15**) alcohols (as determined by ^{1}H-n.m.r. integration of the two OH triplets) as a colorless oil (90.2 mg, 34%); R_F 0.25 (1:1:1 petroleum ether–ether–dichloromethane); ν_{max}^{film} 3600–3300 (br. OH), 3085, 3060, 3030 (alkene, arom.), 2910, 2870 (CH_2,CH), 1600, 1580, 1450 (arom. ring), 1360, 1210, 1150–950 (br., OR), 735, and 690 cm^{-1} (monosubst. arom.); ^{1}H-n.m.r. ($CDCl_3$): δ 7.33–7.22 (m, 15 H, Ph), 4.62–4.41 (m, 6 H, 3 OCH_2Ph, no ABq's could be determined), 4.2–4.05 (m, 4 H, H-2,3,4,5), 3.84–3.64 (m, 2 H, sharpens to an app. t. at 3.83 and a dd at 3.70 upon addition of D_2O, H_2-1), 3.61 (m, 2 H, H_2-6), 2.55 (t, 1 H, $J_{1,OH}$ 6.5 Hz, D_2O exchange), and 2.10 (t, 1 H, $J_{1,OH}$ 6.5 Hz, D_2O exchange); ^{13}C-n.m.r. ($CDCl_3$): δ 138.05, 137.94, 137.85, 137.76, 137.67 (s, C quat., OCH_2Ph), 133.14–127.80 (m, $OCH_2C_6H_5$), 84.74, 84.33, 83.88, 83.42, 83.30, 81.92, 80.56, 73.46, 72.13, 72.00, 71.90, 70.27, 70.19, 62.73 (t, C-1 *altro*), and 61.71 (t, C-1 *allo*); m.s. (c.i.): *m/z* 435 (MH^+), 343, 371, 181, 145, 107, and 91.

Anal. Calc. for $C_{27}H_{30}O_5 \cdot H_2O$: C, 72.38; H, 7.09. Found: C, 72.52; H, 6.86.

*2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-*D*-allitol* (**16**) *and* -D-*altritol*[15] (**17**). — *Method A using the crude reaction mixture from the mercury-induced cyclization.* The crude organomercurials (153.2 mg, 0.23 mmol) were dissolved in dichloro-

methane (2.5 mL), and solid benzyltriethylammonium chloride (262 mg, 1.15 mmol) dissolved in 10% NaOH (1.5 mL) was added. The mixture was cooled to 0° and solid $NaBH_4$ (85.1 mg, 2.3 mmol) was added all at once. The reaction was quenched within 2 min by addition of water*. The reaction mixture was diluted with dichloromethane (20 mL), and the layers were separated. The organic layer was washed successively with water (5 mL), saturated NaCl (5 mL), and dried ($MgSO_4$). Filtration and evaporation under reduced pressure gave a yellow oil (48.2 mg, 49%) which, though homogeneous by t.l.c., was an inseparable mixture of diastereomers enriched in the *allo* (**16**) isomer, $[\alpha]_D^{26}$ +24.6° (*c* 1.46, chloroform), R_F 0.16 (9:1:1 petroleum ether–ether–dichloromethane); ν_{max}^{film} 3120, 3100, 3080, 3040 (alkene, arom.), 2940, 2920, 2880 (CH_2,CH,CH_3), 1500, 1450 (arom. ring), 1220, 1150–1050 (br., OR), 740 and 700 cm^{-1} (monosubst. arom.); ^{1}H-n.m.r. ($CDCl_3$): δ 7.39–7.27 (m, 15 H, Ph), 4.65–4.40 (m, 6 H, 3 OCH_2Ph, no ABq's could be determined), 4.15 (m, 1 H, H-2, collapses to a doublet having $J_{2,3}$ 3.7 Hz upon irradiation of CH_3), 4.05 (m, 1 H, H-5), 3.91 (app. d, 1 H, H-3), 3.78 (d, 1 H, $J_{4,5}$ 3.7 Hz, H-4), 3.60 (dABq, 2 H, ν_{AB} 20.94, J_{AB} 9.8, $J_{5,6}$ 6.2 Hz, H-6A,B), 1.35 (br. d, 3 H, $J_{1,2}$ 6.5 Hz, CH_3); ^{1}H-n.m.r. (C_6D_6): δ 1.42 (d, 3 H, $J_{1,2}$ 6.5 Hz, CH_3, *allo*), and 1.35 (d, 3 H, $J_{1,2}$ 6.5 Hz, CH_3, *altro*); ^{13}C-n.m.r. ($CDCl_3$): δ 138.49, 138.34, 138.14 (s, C quat., OCH_2Ph), 128.64–127.73 (m, $OCH_2C_6H_5$), 84.83 (d, C-2), 84.12 (d, C-5), 82.62 (d, C-3), 77.45 (d, C-4), 73.54, 71.71, 71.59 (t, OCH_2Ph), 71.01 (t, C-6), and 14.34 (q, C-1); m.s. (c.i.): *m/z* 419 (MH^+), 327, 181, 147, 133, 117, 107, and 91.

Anal. Calc. for $C_{27}H_{30}O_4$: C, 77.48; H, 7.22. Found: C, 77.21; H, 7.25.

Method B. General procedure for reduction of halogen (I_2, Br_2) and selenium-induced cyclization products. The crude cyclization product was dissolved in dry benzene (from CaH_2) to give a 0.06M solution. A catalytic amount of azoisobutyronitrile (0.05 eq.) was added, followed by excess tributyltin hydride (3.0 eq.). The mixture was refluxed for 45 min under an atmosphere of Ar. Benzene was removed *in vacuo* and the mixture diluted with acetonitrile. The acetonitrile layer was shaken with hexane (3 × 5 mL) and the combined hexane layers were discarded. The acetonitrile layer was dried ($MgSO_4$), filtered, and evaporated to give the crude reduction product (**16** and **17**) as a mixture of diastereomers. Yields were 70, 74, and 80% for reduction of the iodomethyl (**3**), bromomethyl (**8**), and phenylselenomethyl (**12**) compounds, respectively.

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*Longer reaction times or higher temperature gave **2** as the major product. These conditions minimized the β-elimination process (10–15%).

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DICHLOROMETHYLENATION OF 1,4-LACTONES. A NEW ACCESS TO 1-DEOXY-1-*C*-METHYL-*C*-GLYCOSYL COMPOUNDS*

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ABSTRACT

Sugar 1,4-lactones reacted with hexamethylphosphorous triamide–tetrachloromethane to give dichloroolefins in one step. These compounds are versatile intermediates. Treatment of these 1,1-dichloro-1,1-dideoxy-3,4,-*O*-isopropylidene derivatives with lithium diisopropylamide gave the corresponding 4-deoxy-3-ulo derivatives. Reduction of the dichloromethylene group gave a methyl group with high stereospecifity. This opens the way to a set of 2,5-anhydro-1-deoxyalditols.

INTRODUCTION

The discovery of *C*-nucleosides and their biological properties[1] prompted the search for the synthesis of *C*-glycosyl compounds. Some methods have been proposed which allowed the introduction of a highly functionalized chain at the anomeric center. The functionality permitted the construction of various nitrogen-containing heterocycles. These syntheses have been the topic of a review[2]. Nevertheless, the formation of a carbon–carbon bond at the anomeric center with a high degree of stereoselectivity remained a problem which has been partially solved in the past few years with the synthesis of recently discovered, highly-complex structures[3] of some natural products. Oxolane and oxane rings present in these structures have been synthetized, as well as model compounds. Several methods have been published, for example the reaction of allylsilanes[4] and enol ethers[5], Claisen[6] and Ferrier[7] rearrangements, the Wittig reaction[8], and the generation of carbanions[9] at C-1 or radical chemistry[10].

Only a few reports of the use of lactones as starting materials for *C*-glycosyl compounds synthesis have been published[11,12]. Sugar lactones are often commercially available or readily obtained from the corresponding alcohol. Nucleophilic additions on the carbonyl group, followed by subsequent dehydration led to the

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TABLE I

DICHLOROMETHYLENATION OF 1,4-LACTONES

Starting compound	*Product*	*Reaction conditions*		*Yield*
		Temp. (°)	*Time (h)*	*(%)*
1	**2**	−30	1	79
4	**5**	−30	1	92
8	**9**	0	3	52
12	**13**	0	4	75
16	**17**	−30	1	67
19	**20**	−30	3	90

formation of a carbon–carbon double bond. If the reagent is able to perform both reactions, the oxygen atom of the lactone may be replaced by a substituted carbon atom.

N, N, N′, N′, N″, N″ - Hexamethylphosphorous triamide - tetrachloromethane ($(Me_2N)_3P$–CCl_4), a reagent known for the activation of sugar hydroxyl groups[13], has been also used for the transformation of a carbonyl into a dihalogenomethylene group. This reaction was applied to some aldehydes and ketones[14]*, including keto sugars[16]. 1,4-Lactones derived from sugars react with $(Me_2N)_3P$–CCl_4 to form dichloroolefins in good yields[17], and we report now some applications of this reaction to the field of deoxy-*C*-glycosyl compounds.

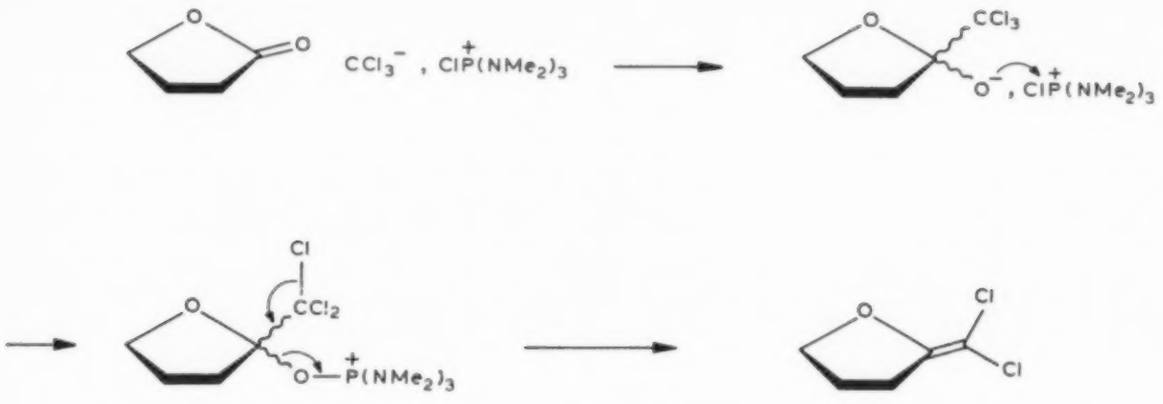
RESULTS AND DISCUSSION

Treatment of some 1,4-lactones with the reagent in dry oxolane at low temperature gave the corresponding dichloroolefins in good yields. The reaction can be performed by slow addition of the phosphine to a solution of carbon tetrachloride at −30°, followed by addition of the lactone, or by adding the phosphine to the mixture of carbon tetrachloride and lactone in dry oxolane with a motor-driven syringe, thus allowing a very slow addition.

The use of carbon tetrabromide instead of carbon tetrachloride gave complex mixtures which darkened rapidly at −30°. The triphenylphosphine–carbon tetrachloride system, which is known to react well with ketones and aldehydes to give dichloroolefins, gave no reaction with 1,4-lactones. This observation supports an ionic mechanism rather than a phosphorane-type mechanism as triphenylphosphine could give phosphorane whereas $(Me_2N)_3P$ could not [18].

The reaction is believed to proceed *via* trichloromethylide formation, followed by condensation of this unstable compound with the carbonyl group of the lactone. Oxytris(dimethylamino)phosphonium salt formation arose from the reaction of the tertiary alcoholate with the chlorophosphonium salt. Subsequent positive halogen

*For a silicon based reagent, see ref. 15.



Scheme 1.

abstraction by the phosphine or the complex phosphine–carbon tetrachloride afforded the dichloromethylene group and hexamethylphosphoric triamide (see Scheme 1). Thus, with sterically hindered lactone as in the D-*ribo* series, condensation of the trichloromethylide anion became sluggish. There is a delicate balance between the nucleophilic attack of the anion and its decomposition, which could explain the excess of phosphine needed and the observed yield. Replacement of the bulky (1,1-dimethylethyl)dimethylsilyl group by acetate led to a better yield of dichloroolefins **13**, this observation supporting our hypothesis. On the other hand, these results demonstrated the excellent chemoselectivity of the reagent, which distinguished between ester and lactone. The mildness of the reaction conditions allowed the use of the acetate, mesylate, or silyl group to protect alcohol groups.

For further transformation of the sugar in the presence of a dichloromethylene group, which may act as a carbonyl protecting group, the stability of this group was examined. Thus, acid hydrolysis of **5** in aqueous acetic acid led to **6** in nearly quantitative yield, and deacetylation of **13** with sodium methoxide gave **15** in the same yield.

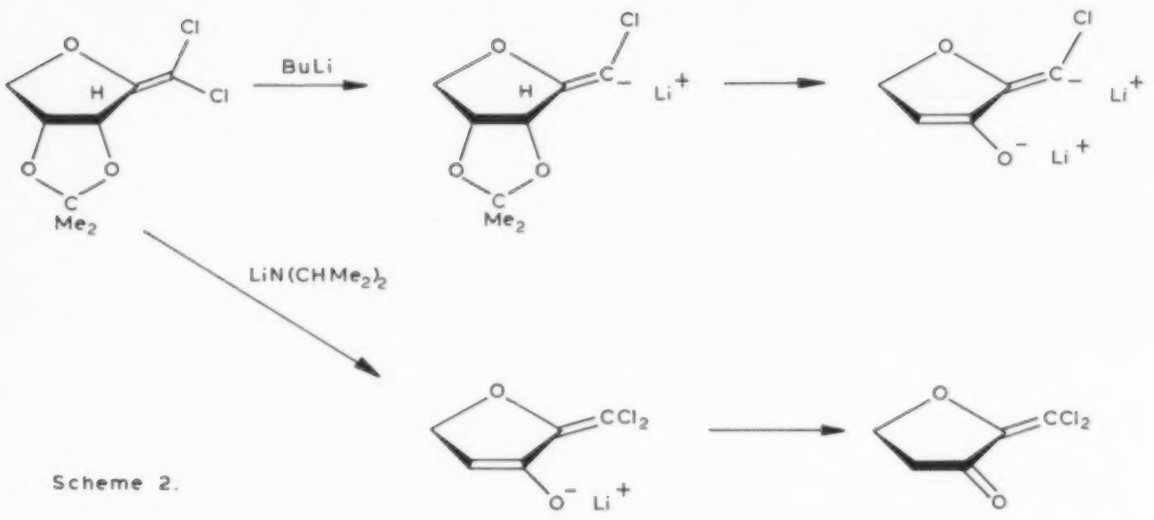
The reduction of the dichloromethylene to a methyl group giving a *cis* arrangement of the methyl and 3,4,-*O*-isopropylidene groups was efficiently achieved

TABLE II

RANEY NICKEL REDUCTION OF DICHLOROMETHYLENE COMPOUNDS

Starting compound	*Product*	*Reaction time (h)*	*Yield (%)*
2	**3**	3	71
5	**7**	2	90
9	**10** + **11**[a]	5	82
13	**14**	5	83
17	**18**	5	72
20	**21**	3	65

[a] 9.1 Ratio by ^{1}H-n.m.r. estimation.



Scheme 2.

by the use of freshly prepared Raney nickel in ethyl acetate. The reaction was completely stereospecific, except in the case of the D-*ribo* derivative **9**. It was possible to detect the *trans* isomer **11** by ^{1}H-n.m.r. spectroscopy although we were unable to isolate **11** in the pure form without contamination of the *cis* isomer **10**. Table II summarizes these results.

Action of strong bases on dichloro compounds was then examined. This investigation began with **5** which, upon treatment with butyllithium, gave a new product. Careful spectral analysis revealed that a mixture of ketones had been obtained (Scheme 2). In fact, two concurrent reactions occured, a metal-to-halogen exchange of one chlorine atom and an H-3* abstraction by butyllithium, thus giving rise to the formation of deoxyketones[19]. The reaction was very difficult to monitor and needed a large excess of alkyllithium and so we eventually turned to other strong bases. Lithium diisopropylamide [$LiN(CHMe_2)_2$] was found to be very efficient, the metal-to-halogen exchange being suppressed. Dichloroolefins were treated with an excess of amide in dry oxolane to give the expected ketones in good yield. Upon treatment of **20** with an excess of amide, both the 3,4-*O*-isopropylidene and 6-*O*-

TABLE III

TREATMENT OF DICHLOROOLEFINS WITH LITHIUM DIISOPROPYLAMIDE

Starting compound	*Product*	*Reaction conditions*		*Yield*
		Temp. (°)	*Time (h)*	*(%)*
2	**22**	−30	2	69
5	**23**	−30	2	90
9	**24**	−30	3	57

*Refers to heptose numbering.

TABLE IV

RANEY NICKEL REDUCTION OF KETONES

Starting compound	Product	Reaction time (h)	Yield (%)
22	**25** + **26** (9:1)	1	70[a]
23	**27** + **28**	2	10 85
24	**29** + **30**	3	65 10

[a] Pure isolated **26**

acetyl groups were removed, thus giving a complex mixture of different ketones.

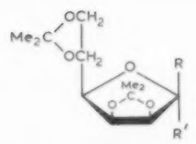
Attempts to protect the starting lactone with the base-stable (1,1-dimethylethyl)dimethylsilyl group were unsuccessful. This transformation opens the way to branched-chain carbohydrate, owing to the possible alkylation of intermediate ketone enolates according to our recent method[20]. The results obtained with lithium diisopropylamide are summarized in Table III.

Finally, we attemped the reduction of the dichloroketones obtained. Raney nickel was found to be very efficient to reduce both double bonds and carbon–chlorine bonds, thus a new route to dideoxy-*C*-glycosyl compounds was opened. Our results are summarized in Table IV.

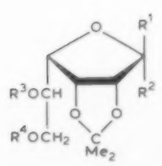
In conclusion, the convenient dichloromethylenation of sugar 1,4-lactones gives a new access to deoxy-*C*-glycosyl- or dideoxy-*C*-glycosyl compounds after Raney nickel reduction. Indeed, the introduced methyl group may be regarded as the C-5′ of a *C*-glycosyl compounds bearing a chiral functionalized appendage of one to three carbon atoms. This may be of interest for N the synthesis of natural products, such as muscarin and furanomycin *i.a.* Compounds such as **2** and **22** are potentially useful in the synthesis of more complex molecules.

EXPERIMENTAL

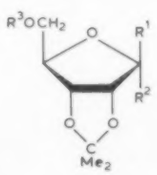
General methods. — Optical rotations were measured with a Perkin–Elmer



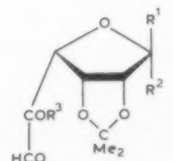
1 R, R′ = O
2 R, R′ = CCl_2
3 R = Me, R′ = H



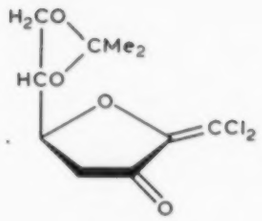
4 R^1, R^2 = O; $R^3 = R^4 = CMe_2$
5 $R^1, R^2 = CCl_2$; $R^3, R^4 = CMe_2$
6 $R^1, R^2 = CCl_2$; $R^3 = R^4$ = H
7 R^1 = H; R^2 = Me



8 R^1, R^2 = O; $R^3 = Bu^tMe_2Si$
9 $R^1, R^2 = CCl_2$; $R^3 = Bu^tMe_2Si$
10 R^1 = H; R^2 = Me; $R^3 = Bu^tMe_2Si$
11 R^1 = Me; R^2 = H; $R^3 = Bu^tMe_2Si$
12 R^1, R^2 = O; R^3 = Ac
13 $R^1, R^2 = CCl_2$; R^3 = Ac
14 R^1 = H; R^2 = Me; R^3 = Ac
15 $R^1, R^2 = CCl_2$; R^3 = H



16 R^1, R^2 = O; R^3 = Ms
17 $R^1, R^2 = CCl_2$; R^3 = Ms
18 R^1 = H; R^2 = Me; R^3 = Ms
19 R^1, R^2 = O; R^3 = Ac
20 $R^1, R^2 = CCl_2$; R^3 = Ac
21 R^1 = H; R^2 = Me; R^3 = Ac



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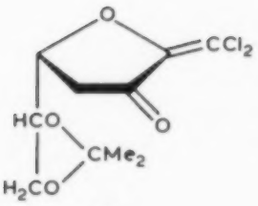

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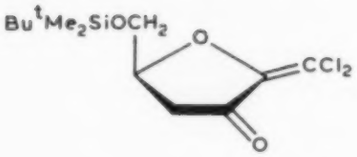

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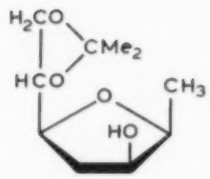

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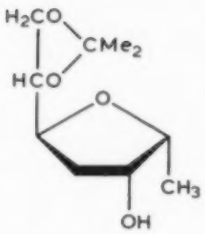

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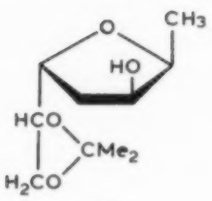

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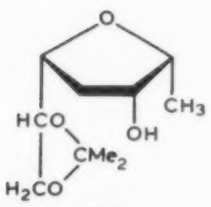

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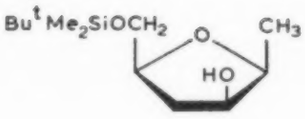

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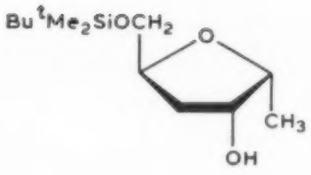

30

141 polarimeter. I.r. spectra were recorded for thin films with a Perkin–Elmer 580 B spectrometer, and ^{1}H-n.m.r. spectra for solutions in (^{2}H)chloroform with tetramethylsilane as the internal standard with a Bruker Aspect 3000 (400 MHz) instrument. T.l.c. was performed on Merck precoated plates of Silica gel 60 and detection was effected by spraying the plates with H_2SO_4 in methanol and heating under an i.r. lamp. Oxolane was distilled immediately prior to use from sodium–benzophenone. N,N,N′,N′,N″,N″-Hexamethylphosphorous triamide was purchased from Aldrich and distilled before use. Raney nickel was prepared according to Burgstahler and Abdel-Rahman[21]. Starting lactones **1**, **4**, **8**, **12**, **16**, and **19** were prepared according to references cited by standard procedures (respectively refs. 22, 23, 11, 24, 25 and 25). Microanalyses were performed by the Service Central de Microanalyses du C.N.R.S. (Vernaison, France): amorphous compounds **2**, **5**, **9**, **13**, **15**, **17**, **24**, **29**, and **30** were unstable and gave unsatisfactory results.

Procedures for dichloromethylenation of lactones. — Method A. To a solution of carbon tetrachloride (1.2 g, 8 mmol) in anhydrous oxolane (30 mL)

under Ar was added dropwise a solution of $(Me_2N)_3P$ (980 mg, 6 mmol) in anhydrous oxolane (10 mL) at −30°. A white precipitate was formed. A solution of the lactone (**1** or **4**: 516 mg, 2 mmol) in oxolane (20 mL) was subsequently added. Stirring was continued for 1 h at −30°. T.l.c. indicated complete transformation of the starting compound. The mixture was then poured into water and the product extracted with diethyl ether (3 × 100 mL). After rapid washing with dilute HCl (10 mL) and water (50 mL), the organic layer was dried ($MgSO_4$) and evaporated. Column chromatography of the residue afforded pure dichloroolefins.

Method B. To a solution of lactone (2 mmol) and carbon tetrachloride (1.2 g, 8 mmol) in anhydrous oxolane (30 mL) under Ar was added over 2 h with a motor-driven syringe (or very slowly) a solution of $(Me_2N)_3P$ (980 mg, 6 mmol) in anhydrous oxolane (10 mL) at the temperature indicated in Table I. The reaction was monitored by t.l.c. If some starting material remained, the treatment was repeated by adding further amount of carbon tetrachloride and phosphine until complete disappearance of starting material. The products were recovered by Method A.

*2,5-Anhydro-1,1-dichloro-1-deoxy-3,4:6,7-di-*O*-isopropylidene-*D*-manno-hept-1-enitol* (**2**). — Yield 512 mg (79%), $[\alpha]_D^{20}$ +172° (*c* 0.5, chloroform), R_F 0.7 (2:1 hexane–ethylacetate) ; ν_{max} 1665 cm^{-1}; ^{1}H-n.m.r. (250 MHz): δ 1.38 (s, 3 H), 1.42 (s, 3 H), 1.45 (s, 3 H), 1.48 (s, 3 H, CMe_2); 4.12 (m, 3 H, H-7, 7′, 5), 4.5 (m, 1 H, H-6), 4.87 (m, 1 H, H-4), and 5.3 (d, 1 H, H-3).

*3,6-Anhydro-7,7-dichloro-7-deoxy-1,2:4,5-di-*O*-isopropylidene-*L*-gluco-hept-6-enitol* (**5**). — Yield 598 mg (92%), $[\alpha]_D^{20}$ −175° (*c* 0.5, chloroform), R_F 0.57 (1:1 hexane–ethylacetate); ν_{max} 1660 cm^{-1}, ^{1}H-n.m.r. (250 MHz): δ 1.37 (s, 3 H), 1.4 (s, 3 H), 1.46 (s, 6 H, CMe_2), 3.75 (dd, 1 H, $J_{1,2}$ 7 $J_{1,1'}$ 8.5 Hz, H-1), 4.19 (dd, 1 H, $J_{3,4}$ 4, $J_{3,2}$ 8.5 Hz, H-3), 4.23 (dd, 1 H, $J_{1',2}$ 7 Hz, H-1′), 4.45 (dd, 1 H, H-2), 4.75 (dd, 1 H, $J_{3,4}$ 4 Hz, H-4), and 5.31 (d, 1 H, $J_{4,5}$ 6 Hz, H-5).

*2,5-Anhydro-1,1-dichloro-1-deoxy-3,4-*O*-isopropylidene-6-*O*-[(1,1-dimethylethyl)dimethylsilyl]-*D*-ribo-hex-1-enitol* (**9**). — Yield 377 mg (51%), $[\alpha]_D^{22}$ −145° (*c* 0.5, chloroform), R_F 0.5 (9:1 hexane–ethyl acetate); ν_{max} 1660 cm^{-1}, ^{1}H-n.m.r.: δ 0.06 (s, 6 H, CH_3Si), 0.88 (s, 9 H, Bu^tSi), 1.4 (s, 3 H), 1.47 (s, 3 H), 3.76 (dd, 1 H, $J_{5,6}$ 1.5, $J_{6,6'}$ 11 Hz, H-6), 3.84 (dd, 1 H, $J_{5,6'}$ 2.5 Hz, H-6′), 4.6 (t, 1 H, H-5), 4.81 (d, 1 H, $J_{3,4}$ 6 Hz, H-4), and 5.23 (d, 1 H, H-3).

*6-*O*-Acetyl-2,5-anhydro-1,1-dichloro-1-deoxy-3,4-*O*-isopropylidene-*D*-ribo-hex-1-enitol* (**13**). — Yield 445 mg (75%), $[\alpha]_D^{22}$ −154° (*c* 0.5, chloroform), R_F 0.56 (2:1 hexane–ethyl acetate); ν_{max} 1750, 1665 cm^{-1}; ^{1}H-n.m.r.: δ 1.4 (s, 3 H), 1.5 (s, 3 H, CMe_2), 2.1 (s, 3 H, $COCH_3$), 4.1 (dd, 1 H, $J_{6,5}$ 3.5, $J_{6,6'}$ 12 , H-6), 4.35 (dd, 1 H, $J_{5,6'}$ 3.5 Hz, H-6), 4.75 (m, 2 H, H-4,5), and 5.3 (d, 1 H, $J_{3,4}$ 6 Hz, H-3).

*2,5-Anhydro-1,1-dichloro-1-deoxy-3,4:7,8-di-*O*-isopropylidene-6-*O*-methanesulfonyl-*D*-glycero-*D*-gluco-oct-1-enitol* (**17**). — Yield 290 mg (67%), $[\alpha]_D^{22}$ −112° (*c* 0.5, chloroform), R_F 0.45 (3:2 hexane–ethyl acetate); ν_{max} 1660 cm^{-1}, ^{1}H-n.m.r.: δ 1.38 (s, 3 H), 1.4 (s, 3 H), 1.42 (s, 3 H), 1.45 (s, 3 H, CMe_2), 3.15 (s, 3 H, SO_2CH_3), 4.0–4.2 (m, 4 H, H-5, 7,8,8′), 4.8 (dd, 1 H, $J_{4,5}$ 4, $J_{3,4}$ 6 Hz, H-4), 5.08

(dd, 1 H, $J_{6,7}$ 4, $J_{5,6}$ 9 Hz, H-6), and 5.33 (d, 1 H, H-3).

*6-O-Acetyl-2,5-anhydro-1,1-dichloro-1-deoxy-3,4:7,8-di-O-isopropylidene-*D-glycero-D-gluco-*oct-1-enitol* (**20**). — Yield 715 mg (90%), m.p. 77° (hexane), $[\alpha]_D^{22}$ −85° (*c* 0.5, chloroform), R_F 0.55 (2:1 hexane–ethyl acetate); ν_{max} 1745, 1665 cm^{-1}, ^{1}H-n.m.r.: δ 1.3 (s, 3 H), 1.39 (s, 3 H), 1.42 (s, 3 H), 1.48 (s, 3 H, CMe_2), 2.1 (s, 3 H, $COCH_3$), 3.97 (dd, 1 H, $J_{7,8}$ 6, $J_{8,8'}$ 9 Hz, H-8), 4.05 (dd, 1 H, $J_{7,8'}$ 6.5 Hz, H-8′), 4.2 (dd, 1 H, $J_{4,5}$ 3.5, $J_{5,6}$ 7 Hz, H-5), 4.3 (dd, 1 H, $J_{6,7}$ 5.5 Hz, H-7), 4.8 (dd, 1 H, $J_{3,4}$ 5.5, $J_{4,5}$ 3.5 Hz, H-4), 5.3 (d, 1 H, H-3), and 5.55 (dd, 1 H, H-6).

Anal. Calc. for $C_{16}H_{22}Cl_2O_7$: C, 48.38; H, 5.58; Cl, 17.85. Found: C, 48.21; H, 5.65; Cl, 18.28.

*3,6-Anhydro-7,7-dichloro-7-deoxy-4,5-O-isopropylidene-*L-gluco-*hept-6-enitol* (**6**). — Compound **5** (230 mg, 0.7 mmol) was dissolved in aqueous acetic acid (40 mL, 7:3, v:v). The mixture was heated at 50°. T.l.c. monitoring showed complete disappearance of starting material after 1 h. The solvent was evaporated and, after three codistillations with toluene, the residue was directly chromatographed on silica gel; yield 190 mg (95%); m.p. 118°, $[\alpha]_D^{20}$ −200° (*c* 0.5, chloroform), R_F 0.33 (2:3 hexane–ethyl acetate); ν_{max} 3600 cm, 1660 cm^{-1}, ^{1}H-n.m.r.: δ 1.4 (s, 3 H), 1.48 (s, 3 H, CMe_2), 2.5 (b.m., 1 H, CH_2OH), 3.15 (m, 1 H, CHOH), 3.8 (dd, 1 H, $J_{7,7'}$ 11.5, $J_{6,7}$ 4.5 Hz, H-7), 3.9 (dd, 1 H, $J_{6,7'}$ 3.5, H-7′), 4.15 (q, 1 H, $J_{5,6}$ 7 Hz, H-6), 4.28 (dd, 1 H, $J_{4,5}$ 3.5 Hz, H-5), 4.88 (dd, 1 H, $J_{3,4}$ 6 Hz, H-4), and 5.35 (d, 1 H, H-3).

Anal. Calc. for $C_{10}H_{14}Cl_2O_5$: C, 42.13; H, 4.95; Cl, 24.87. Found: C, 41.77; H, 4.98; Cl, 23.98.

*2,5-Anhydro-1,1-dichloro-1-deoxy-3,4-O-isopropylidene-*D-ribo-*hex-1-enitol* (**15**). — Compound **13** (450 mg, 1.5 mmol) was dissolved in dry methanol (40 mL). A catalytic amount of Na (3 mg) was then added. After 3 h of stirring at room temperature, the mixture was made neutral with Dowex 50W (H^+). Filtration and evaporation gave pure **15** (380 mg, 95%), $[\alpha]_D^{20}$ −128° (*c* 0.5, chloroform), R_F 0.4 (2:1 hexane–ethyl acetate); ν_{max} 3600, 1665 cm^{-1}, ^{1}H-n.m.r.: δ 1.2 (s, 3 H), 1.3 (s, 3 H, CMe_2), 3.05 (m, 1 H, OH), 3.7 (dd, 1 h, $J_{6,6'}$ 7 $J_{5,6}$ 3 Hz, H-6), 3.85 (dd, 1 H, $J_{5,6'}$ 2.5 Hz, H-6′), 4.6 (s, 1 H, H-5), 4.8 (d, 1 H, $J_{3,4}$ 6 Hz, H-4), and 5.3 (d, 1 H, H-3).

Procedure for Raney nickel reduction. — The dichloromethylene derivative (1 mmol) was dissolved in dry ethyl acetate. About 200 mg of freshly prepared Raney nickel, previously washed with ethyl acetate, were added and the mixture vigourously stirred until complete transformation of the starting material (t.l.c. monitoring). The mixture was filtered through a pad of Celite and the filtrate evaporated. Column chromatography afforded pure products.

*2,5-Anhydro-1-deoxy-3,4:6,7-di-O-isopropylidene-*D-glycero-D-manno-*heptitol* (**3**). — Yield 183 mg (71%), $[\alpha]_D^{20}$ −20.8° (*c* 0.5, chloroform), R_F 0.47 (3:2 hexane–ethyl acetate); ^{1}H-n.m.r.: δ 1.3 (d, 3 H, *J* 6 Hz, Me), 1.33 (s, 3 H), 1.36 (s, 3 H), 1.43 (s, 3 H), 1.47 (s, 3 H, CMe_2), 3.47 (dd, 1 H, $J_{4,5}$ 3.5 $J_{5,6}$ 7.5 Hz, H-5), 3.64 (m, 1 H, H-1), 4.05 (m, 2 H, H-7,7′), 4.38 (m, 1 H, H-5), 4.55 (dd, 1 H, $J_{3,4}$ 6, $J_{3,2}$ 3.5 Hz, H-3), and 4.73 (dd, 1 H, H-4).

Anal. Calc. for $C_{13}H_{22}O_5$: C, 60.45; H, 8.59. Found: C, 60.10; H, 8.50.

*3,6-Anhydro-7-deoxy-1,2:4,5-di-*O*-isopropylidene-*D*-glycero-*L*-gluco-heptitol* (**7**). — Yield 232 mg (90%), $[\alpha]_D^{20}$ +21° (*c* 0.5, chloroform), R_F 0.53 (3:2 hexane–ethyl acetate); ^{1}H-n.m.r.: δ 1.3 (s, 3 H, CMe_2), 1.38 (d, 3 H, *J* 6 Hz, H-7), 1.59 (s, 3 H, CMe_2), 1.63 (s, 6 H, CMe_2), 3.53 (dd, 1 H, $J_{3,4}$ 4, $J_{2,3}$ 8 Hz, H-3), 3.56 (m, 2 H, H-6,1), 4.23 (dd, 1 H, $J_{1,2}$ 7, $J_{1,1'}$ 8.5 Hz, H-1′), 4.41 (q, 1 H, H-2), 4.78 (dd, 1 H, $J_{5,6}$ 4, $J_{4,5}$ 6.5 Hz, H-2), and 4.83 (dd, 1 H, H-5).

Anal. Calc. for $C_{13}H_{22}O_5$: C, 60.45; H, 8.59. Found: C, 60.19; H, 8.53.

*2,5-Anhydro-1-deoxy-3,4-*O*-isopropylidene-6-*O*-[(1,1-dimethylethyl)dimethylsilyl]-*D*-altritol* (**10**). — Yield 247 mg (82%), $[\alpha]_D^{22}$ −4.4° (*c* 0.5, chloroform), R_F 0.35 (9:1 ether–hexane); ^{1}H-n.m.r.: δ 0.06 (s, 6 H, Me_2Si), 0.9 (s, 9 H, Bu^tSi), 1.27 (d, 3 H, *J* 6 Hz, H-1), 1.36 (s, 3 H, CMe_2), 1.51 (s, 3 H, CMe_2), 3.3 (m, 2 H, H-6,6′), 4.05 (t, 1 H, $J_{5,6}$ 4 Hz, H-5), 4.2 (dq, 1 H, $J_{2,3}$ 4 Hz, H-2), 4.59 (dd, 1 H, $J_{3,4}$ 6.5 Hz, H-3), and 4.81 (d, 1 H, H-4).

*6-*O*-Acetyl-2,5-anhydro-1-deoxy-3,4-*O*-isopropylidene-*D*-altritol* (**14**). — Yield 191 mg (83%), $[\alpha]_D^{22}$ +9.7° (*c* 0.5, chloroform), R_F 0.45 (2:1 hexane–ethyl acetate); ν_{max} 1740 cm^{-1}; ^{1}H-n.m.r.: δ 1.3 (d, 3 H, J 6.5 Hz, H-1), 1.35 (s, 3 H), 1.55 (s, 3 H, CMe_2), 2.1 (s, 3 H, CH_3CO), 4.0 (dd, 1 H, $J_{6,6'}$ 11.5, $J_{5,6}$ 5 Hz, H-6), 4.1 (dd, 1 H, $J_{2,3}$ 3.5 Hz, H-2), 4.15 (dd, 1 H, $J_{5,6'}$ 6.5 Hz, H-6′), 4.25 (t, 1 H, H-5), and 4.6 (m, 2 H, H-3,4).

Anal. Calc. for $C_{11}H_{18}O_5$: C, 57.39; H, 7.82. Found: C, 56.96; H, 7.92.

*2,5-Anhydro-1-deoxy-3,4:7,8-di-*O*-isopropylidene-6-*O*-methylsulfonyl-*D*-erythro-*L*-galacto-octitol* (**18**). — Yield 263 mg (72%), $[\alpha]_D^{22}$ +2.2° (*c* 0.5, chloroform), R_F 0.30 (3:2 hexane–ethyl acetate); ^{1}H-n.m.r.: δ 1.29 (d, 3 H, J 6 Hz, H-1), 1.31 (s, 3 H), 1.37 (s, 3 H), 1.48 (s, 3 H, CMe_2), 3.1 (s, 3 H, SO_3CH_3), 3.5 (dd, 1 H, $J_{4,5}$ 3.5 $J_{5,6}$ 9 Hz, H-4), 3.63 (dq, 1 H, $J_{2,3}$ 3.5, *J* 6 Hz, H-2), 4.06 (m, 2 H, H-8,8′), 4.37 (dt, 1 H, $J_{7,8}$ 6.5, $J_{7,8'}$ 6.5 Hz, H-7), 4.6 (dd, 1 H, $J_{3,4}$ 6 Hz, H-3), 4.68 (dd, 1 H, H-3), and 5.08 (dd, 1 H, $J_{6,7}$ 4 Hz, H-6).

Anal. Calc. for $C_{15}H_{26}O_8S$: C, 49.17; H, 7.15; S, 8.75. Found: C, 48.92; H, 7.09; S, 8.50.

*6-*O*-Acetyl-2,5-anhydro-1-deoxy-3,4:7,8-di-*O*-isopropylidene-*D*-erythro-*L*-galacto-octitol* (**21**). — Yield 214 mg (65%), $[\alpha]_D^{20}$ +6.9° (*c* 0.5, chloroform), R_F 0.47 (1:1 hexane–ethyl acetate); ν_{max} 1740 cm^{-1}; ^{1}H-n.m.r.: δ 1.29 (s, 3 H, H-1), 1.30 (s, 3 H), 1.35 (s, 3 H), 1.42 (s, 3 H), 1.49 (s, 3 H, CMe_2), 2.15 (s, 3 H, CH_3CO), 3.48 (dd, 1 H, $J_{4,5}$ 3.5, $J_{5,6}$ 7 Hz, H-5), 3.6 (m, 1 H, *J* 6, $J_{2,3}$ 3.5 Hz, H-2), 4.0 (m, 2 H, $J_{7,8}$ 8, $J_{7,8'}$ 7, $J_{8,8}$ 9 Hz, H-8,8′), 4.35 (m, 1 H, $J_{6,7}$ 4.5 Hz, H-7), 4.6 (dd, 1 H, $J_{3,4}$ 6 Hz, H-3), 4.67 (dd, 1 H, H-4), and 5.53 (dd, 1 H, H-6).

Anal. Calc. for $C_{16}H_{26}O_7$: C, 58.17; H, 7.87. Found: C, 58.80; H, 8.07.

General procedure for ketone formation with lithium diisopropylamide. — Dichloroolefin (1 mmol) was dissolved in dry oxolane (20 mL) under Ar at −30°. Lithium diisopropylamide (2.2 mmol) solution [prepared at 0° from diisopropylamine (220 mg, 2.2 mmol) and butyllithium (2.5M solution, 0.9 mL) in dry oxolane (20 mL) at 0°] was added dropwise over 10 min. After complete disappearence of starting compound (t.l.c. monitoring), the mixture was hydrolyzed with a saturated

ammonium chloride solution (50 mL). Extraction with ether (3 × 100 mL), washing with water, drying (Na_2SO_4), and evaporation afforded a crude product which was chromatographed on a silica gel column.

*2,5-Anhydro-1,1-dichloro-1,4-dideoxy-6,7-*O*-isopropylidene*-D-erythro-*hex-1-enitol-3-ulose* (**22**). — Yield 184 mg (69%), m.p. 83–85° (hexane), $[\alpha]_D^{20}$ −27° (*c* 0.5, chloroform), R_F 0.48 (2:1 hexane–ethyl acetate); υ_{max} 1740, 1600 cm^{-1} ^{1}H-n.m.r. δ 1.35 (s, 3 H), 1.45 (s, 3 H) CMe_2, 2.85 (t, 2 H, $J_{4,5}$ 7.5, $J_{4',5}$ 5.5 Hz, H-4,4'), 3.85 (dd, 1 H, $J_{7,7'}$ 9, $J_{6,7}$ 5 Hz, H-7), 4.2 (dd, 1 H, $J_{6,7'}$ 6.5 Hz, H-7'), 4.35 (m, 1 H, $J_{5,6}$ 5 Hz, H-6), and 4.6 (m, 1 H, H-5).

Anal. Calc. for $C_{10}H_{12}Cl_2O_4$: C, 44.97; H, 4.53; Cl, 26.55. Found: C, 44.87; H, 4.44; Cl, 25.71.

*2,5-Anhydro-1,1-dichloro-1,4-dideoxy-6,7-*O*-isopropylidene*-D-threo-*hex-1-enitol-3-ulose* (**23**). — Yield 240 mg (90%), m.p. 89° (hexane), $[\alpha]_D^{22}$ +26.6° (*c* 0.5, chloroform), R_F 0.44 (2:1 hexane–ethyl acetate); υ_{max} 1740, 1600 cm^{-1}; ^{1}H-n.m.r.: δ 1.3 (s, 6 H, CMe_2), 2.75 (dd, 1 H, $J_{4,5}$ 4.5, $J_{4,4'}$ 18 Hz, H-4), 2.97 (dd, 1 H, $J_{4',5}$ 8.5 Hz, H-4'), 4.1 (dd, 2 H, $J_{6,7}$ 7, $J_{6,7'}$ 2.5 Hz, H-7,7'), 4.25 (m, 1 H, $J_{5,6}$ 2.5 Hz, H-6), and 4.75 (m, 1 H, H-5).

Anal. Calc. for $C_{10}H_{12}Cl_2O_4$: C, 44.97; H, 4.53; Cl, 26.55. Found: C, 44.81; H, 4.56; Cl, 25.96.

*2,5-Anhydro-1,1-dichloro-1,4-dideoxy-6-*O*-[(1,1-dimethylethyl)dimethylsilyl]-*D-glycero-*hex-1-enitol-3-ulose* (**24**). — Yield 160 mg (57%), $[\alpha]_D^{20}$ −24.8° (*c* 0.5, chloroform), R_F 0.48 (4:1 hexane–ethyl acetate); υ_{max} 1740, 1600 cm^{-1}; ^{1}H-n.m.r.: δ 0.1 (s, 6 H, Me_2Si), 0.8 (s, 9 H, Bu^t), 2.80 (dd, 1 H, $J_{4,4'}$ 13, $J_{4,5}$ 8 Hz, H-4), 2.86 (dd, 1 H, $J_{4',5}$ 5 Hz, H-4'), 3.70 (dd, 1 H, $J_{6,6'}$, 11.5, $J_{5,6}$ 2 Hz, H-6), 4.05 (dd, 1 H, $J_{5,6'}$ 2.5 Hz, H-6'), and 4.75 (m, 1 H, H-5).

The above ketones (1 mmol) were hydrogenated over Raney nickel as already described and isolated in the same way.

*2,5-Anhydro-1,4-dideoxy-6,7-*O*-isopropylidene*-D-gluco-*hepitol* (**25**). — Yield 141 mg (70%), $[\alpha]_D^{22}$ +16.7° (*c* 0.5, chloroform), R_F 0.42 (1:1 hexane–ethyl acetate); υ_{max} 3600 cm^{-1}; ^{1}H-n.m.r.: δ 1.3 (d, 3 H, *J* 6.5 Hz, H-1), 1.4 (s, 3 H), 1.5 (s, 3 H, CMe_2), 1.95 (dd, 1 H, $J_{4,4'}$ 14, $J_{4,5}$ 3 Hz, H-4), 2.3 (m, 1 H, $J_{4',5}$ 10, $J_{3,4'}$ 5 Hz, H-4'), 3.3 (m, 1 H, OH), 3.58 (q, 1 H, $J_{7,7'}$ 8, $J_{6,7}$ 6.5 Hz, H-7), 3.8 (dq, 1 H, $J_{2,3}$ 2.5 Hz, H-2), 3.95 (d, 1 H, $J_{3,4}$ 5 Hz, H-3), 4.1 (m, 2 H, $J_{6,7'}$ 2.5, $J_{5,6}$ 6 Hz, H-5,7'), and 4.4 (m, 1 H, H-6).

Anal. Calc. for $C_{10}H_{18}O_4$: C, 59.40; H, 8.91. Found: C, 59.22; H, 8.65.

*2,5-Anhydro-1,4-dideoxy-6,7-*O*-isopropylidene*-D-altro-*heptitol* (**26**). — Pure **27** was not obtained without contamination of **26**. The proportion was determined by integration of ^{1}H-n.m.r. signals of the crude mixture of **25** and **26**.

*2,5-Anhydro-1,4-dideoxy-6,7-*O*-isopropylidene*-D-galacto-*heptitol* (**27**). - Yield 19 mg (10%), $[\alpha]_D^{20}$ +10.5° (*c* 0.5, chloroform), R_F 0.24 (1:1 hexane–ethyl acetate); υ_{max} 3600 cm^{-1}; ^{1}H-n.m.r.: δ 1.25 (d, 3 H, *J* 7 Hz, H-1), 1.37 (s, 3 H), 1.44 (s, 3 H, CMe_2), 1.82 (ddd, 1 H, $J_{4,4'}$ 13, $J_{3,4}$ 2.5, $J_{4,5}$ 6 Hz, H-4), 1.9 (ddd, 1 H, $J_{3,4'}$ 6.5, $J_{4',5}$ 9 Hz, H-4'), 2.0 (m, 1 H, OH), 3.7 (dd, 1 H, $J_{7,7'}$ 8, $J_{6,7}$ 7 Hz, H-7), 3.9 (m,

1 H, $J_{2,3}$ 3.5 Hz, H-2), and 4–4.2 (m, 4 H, H-3,5,6,7′).

Anal. Calc. for $C_{10}H_{18}O_4$: C, 59.40; H, 8.91. Found: C, 59.18; H, 8.75.

*2,5-Anhydro-1,4-dideoxy-6,7-*O*-isopropylidene-*D*-ido-heptitol* (**28**). — Yield 171 mg (85%), $[\alpha]_D^{20}$ −28.6° (*c* 0.5, chloroform), R_F 0.34 (1:1 hexane–ethyl acetate); υ_{max} 3600 cm^{-1}; ^{1}H-n.m.r.: δ 1.27 (d, 3 H, *J* 6 Hz, H-1), 1.4 (s, 3 H), 1.47 (s, 3 H, CMe_2), 1.95 (dd, 1 H, $J_{4,4'}$ 14, $J_{3,4}$ 2.5 Hz, H-4), 2.4 (dd, 1 H, $J_{4',5}$ 4,$J_{3,4'}$ 9 Hz, H-4′), 3.63 (m, 1 H, OH), 3.85 (m, 1 H, $J_{2,3}$ 2.5 Hz, H-2), 3.94 (m, 1 H, H-3), and 3.95–4.1 (m, 4 H, H-5,6,7,7′).

Anal. Calc. for $C_{10}H_{18}O_4$: C, 59.40; H, 8.91. Found: C, 59.27; H, 8.70.

*2,5-Anhydro-1,4-dideoxy-6-*O*-[(1,1-dimethylethyl)dimethylsilyl]-*D*-xylo-hexitol* (**29**). — Yield 160 mg (65%), $[\alpha]_D^{20}$ +37° (*c* 0.5, chloroform), R_F 0.51 (2:1 hexane–ethyl acetate); υ_{max} 3600 cm^{-1}; ^{1}H-n.m.r.: δ 0.13 (2 s, 6 H, Me_2Si), 0.92 (s, 9 H, Bu^t), 1.26 (d, 3 H, *J* 6.5 Hz, H-1), 1.94 (dd, 1 H, $J_{4,5}$ 2.5 Hz, H-4), 2.35 (ddd, 1 H, $J_{4',3}$ 5, $J_{4',5}$ 10, $J_{4,4'}$ 14 Hz, H-4′), 3.5 (dd, 1 H, $J_{5,6}$ 1.5, $J_{5,6'}$ 11 Hz, H-5), 3.82 (m, 3 H, H-2,3,5), 3.9 (m, 1 H, OH), and 4.18 (ddd, 1 H, H-5).

*2,5-Anhydro-1,4-dideoxy-6-*O*-[(1,1-dimethylethyl)dimethylsilyl]-*D*-arabino-hexitol* (**30**). — Yield 24 mg (10%), $[\alpha]_D^{20}$ −9.8° (*c* 0.5, chloroform), R_F 0.30 (2:1 hexane–ethyl acetate); υ_{max} 3600 cm^{-1}; ^{1}H-n.m.r.: δ 0.06 (s, 6 H, $SiCH_3$), 0.85 (s, 9 H, Bu^t), 1.15 (d, 3 H, *J* 6 Hz, H-1), 1.6 (m, 1 H, OH), 1.79 (ddd, 1 H, $J_{4,4'}$ 13, $J_{3,4}$ 3, $J_{4,5}$ 6.5 Hz, H-4), 2.0 (ddd, 1 H, $J_{3,4'}$, 6.5 $J_{4',5}$8 Hz, H-4′), 3.6 (d, 2 H, $J_{5,6} = J_{5,6'}$ = 4.5 Hz, H-6,6′), 3.82 (dq, 1 H, $J_{2,3}$ 3.5 Hz, H-2), 3.92 (m, 1 H, H-3), and 4.15 (m, 1 H, H-5).

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STEREOSELECTIVE SYNTHESIS OF *C*-GLYCOSYL COMPOUNDS *via* MICHAEL ADDITION OF TRIMETHYLSILYL ENOL ETHERS AND ENAMINES TO HEX-1-ENOPYRAN-3-ULOSES

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ABSTRACT

The titanium(IV)-catalyzed addition of trimethylsilyl enol ethers to 2,4,6-tri-*O*-acylhex-1-enopyran-3-uloses (**3** and **4**) gave stereoselectively 3,6-di-*O*-acyl-4-deoxy-β-D-*glycero*-hex-3-enopyranosyl-2-ulose derivatives. The formation of the *C*-glycosyl bond was accompanied by a 2⟶3 acyl shift, followed by the elimination of the 4-acyloxy substituent. Similarly, the reaction of 1-pyrrolidinocyclohexene with **3** and **4** also led stereoselectively to 2-(2,4,6-tri-*O*-acyl-β-D-*ribo*-hexopyranosyl)cyclohexanones. In this Michael addition, among the eight possible diastereomers, only one was formed. The high stereocontrol of both *C*-glycosyl compound syntheses is explained in terms of cyclic transition complexes **A** and **C**.

INTRODUCTION

The synthesis of *C*-glycosyl compounds is receiving increasing attention owing to the number of important natural products possessing *C*-glycosyl bonds, *e.g.*, the *C*-nucleosides[1] and *C*-glycosylflavonoids[2]. Furthermore, synthetic *C*-glycosyl compounds represent interesting chiral synthons, suitable for the synthesis of complex molecules, since they contain a large number of chiral centers and functional groups. For these reasons, new methods for the synthesis of these compounds have been recently developed. Whereas the earlier methods only allowed the introduction of one C-atom, *e.g.*, *via* cyanide[3], the new procedures open up ways to connect larger structures at C-1. Most of these *C*-glycosyl compound syntheses involve the attack of *C*-nucleophiles at the anomeric center of glycosyl halides, lactones[5], or thioglycosides[6]. Another *C*-glycosyl compound synthesis utilizes the addition of glycosyl adicals to double-bond systems[7]. A new flexible concept is based on the "Umpolung" of the chemical reactivity at the anomeric center. Carbanions of 1-deoxy-1-nitro-monosaccharides[8] and, more generally, glycosyllithium compounds[9] have been converted successfully into C-glycosyl compounds by treatment with various electrophiles.

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1 R = Ac
2 R = Me_3CCO

3 R = Ac
4 R = Me_3CCO

RESULTS AND DISCUSSION

In this report, we describe a new method for the synthesis of highly functionalized C-glycosyl compounds consisting of the reaction of 2,4,6-tri-*O*-acetyl- (**3**) and 2,4,6-tri-*O*-pivaloyl-1-deoxy-D-*erythro*-hex-1-enopyran-3-ulose (**4**) with trimethylsilyl enol ethers[10]. The acyl-protected enuloses **3** and **4**, which act as the Michael acceptors in these Mukaiyama reactions[11], were best obtained from the corresponding 1,2,4,6-tetra-*O*-acylglycopyranoses (**1** and **2**) by means of the oxidation of the free OH-3 with dimethyl sulfoxide and acetic anhydride or chlorosulfonyl isocyanate in dichloromethane[12]. In compounds **3** and **4**, the orbital-controlled reacting electrophilic terminus of the α,β-unsaturated carbonyl system is located at the anomeric carbon atom. In contrast to alcohols, which cannot be added to this center stereoselectively[1], the trimethylsilyl enol ethers of ketones **5–8**, aldehyde **9**, and ester **10** reacted highly stereoselectively, in the presence of titanium(IV) catalyst, with the acetyl-protected enulose **3** to form the *C*-glycosyl compounds **11–17**. The reactions took place in dichloromethane at $-78°$ in the presence of titanium(IV) chloride or titanium(IV) chloride–titanium(IV) isopropylate. The reactions were accompanied by an intensive red or orange color and could be monitored by t.l.c.. The nucleophilic addition of the silyl enol ether is apparently followed by a 2→3 acyl shift and subsequent elimination of the acyloxy-4 substituent. After the reaction was finished, the titanium complex was removed by sodium carbonate and, if necessary, the *C*-glycosyl compounds were purified by flash chromatography. The results are summarized in Table I.

As shown in Table I, the reaction of **3** with cyclohexenyl trimethylsilyl ether **5** gave a *C*-glycosyl compound **11** having two new chiral centers (C-1,2′). Among four possible diastereomers, only one was formed in high yield. Analogously, the trimethylsilyl enol ethers of acetophenone (**7**), acetone (**8**), isobutyraldehyde (**9**), and *tert*butyl acetate (**10**) stereospecifically gave **13–16** which, on the basis of their ^{1}H-n.m.r. spectra, have the β-D configuration.

In the reaction of the cyclopentenyl trimethylsilyl ether **6**, a second diastereomer **13** was formed beside the main product **12**. This by-product presumably also has the β-D configuration at the anomeric center, but an opposite configuration relative to **12** at glycosylated C-2′. The cyclopentyl derivative **6** is relatively planar. This property may cause the lower stereocontrol during the approach to **3** as the

TABLE I

SYNTHESIS OF COMPOUNDS 11-16 FROM TRIMETHYLSILYL ENOL ETHERS AND 2,4,6-TRI-*O*-ACETYL-1-DEOXY-D-*erythro*-HEX-1-ENOPYRAN-3-ULOSE (3)[a]

Trimethylsilyl enol ether	*C-Glycosyl compound*	*Ratio of $TiCl_4$ to Ti isopropylate*	*Reaction time (h)*	*Yield (%)*
5	**11**	1:0	0.5	90
6	**12**[b]	1:0	0.5	55[b]
7	**13**	2:1	4	76
8	**14**	2:1	20	50
9	**15**	2:0	17	47
10	**16**	1:0	17	40

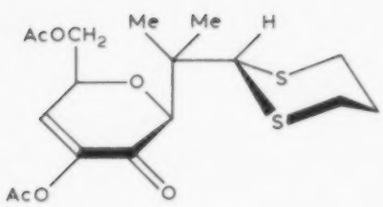
[a]In dichloromethane at −78°. [b]A 5:1 mixture of diastereomers, see Results and Discussion, and Experimental sections.

5 $R^1, R^2 = -(CH_2)_4-, R^3 = H$
6 $R^1, R^2 = -(CH_2)_3-, R^3 = H$
7 $R^1 = Ph, R^2 = R^3 = H$
8 $R^1 = Me, R^2 = R^3 = H$
9 $R^1 = H, R^2 = R^3 = Me$
10 $R^1 = OBu^t, R^2 = R^3 = H$

11 $R^1, R^2 = -(CH_2)_4-, R^3 = H$
12 $R^1, R^2 = -(CH_2)_3-, R^3 = H$
13 $R^1 = Ph, R^2 = R^3 = H$
14 $R^1 = Me, R^2 = R^3 = H$
15 $R^1 = H, R^2 = R^3 = Me$
16 $R^1 = OBu^t, R^2 = R^3 = H$

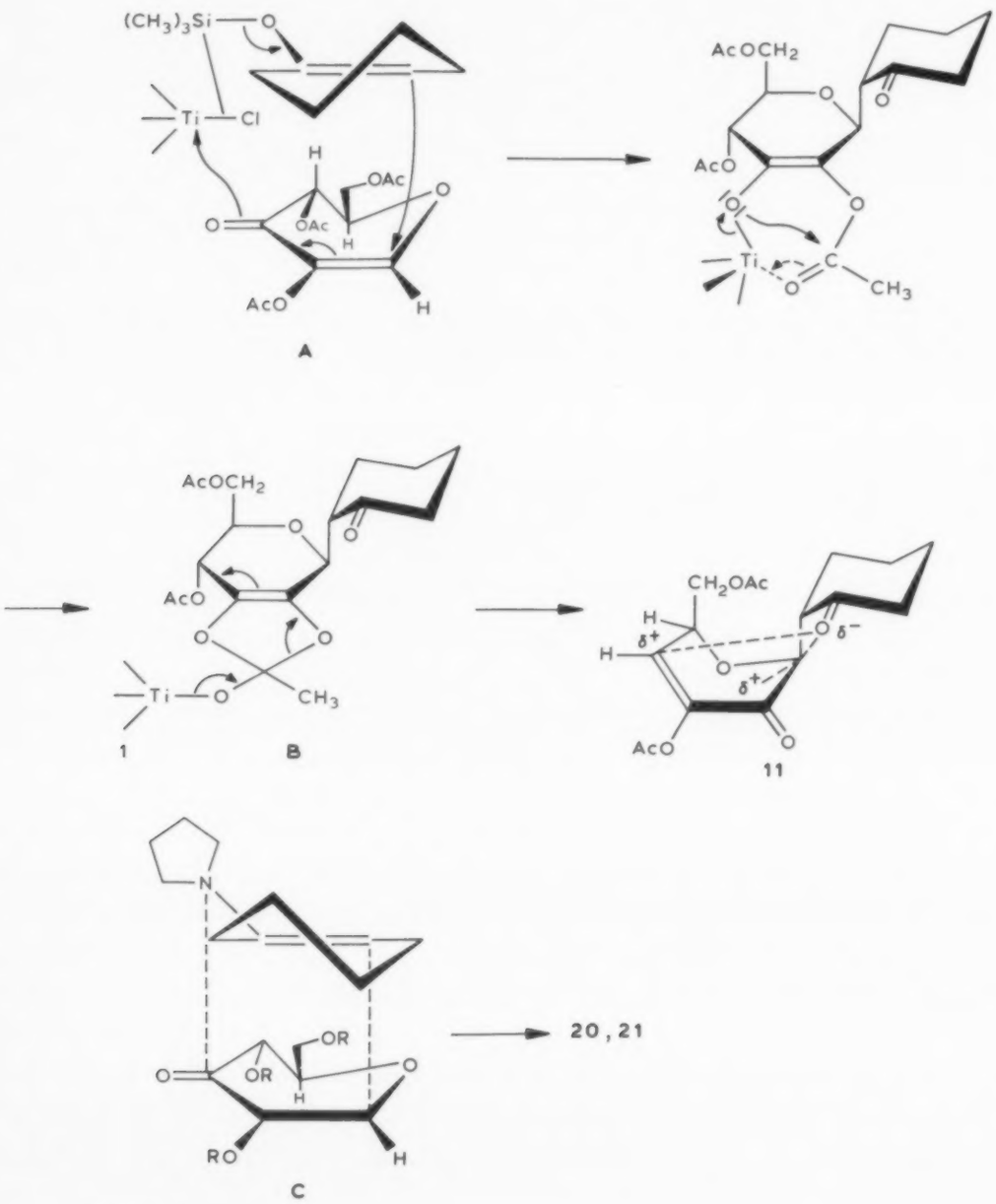
reacting partner. The *C*-glycosyl compound **15** obtained from isobutyraldehyde retained traces of unpolar impurities. Therefore, it was converted into the dithioacetal **17** with 1,3-propanedithiol.

The n.m.r. spectroscopic determination of the structure of the synthesized *C*-glycosyl compounds is rather problematic owing to the lack of the commonly evaluated H-1–H-2 coupling. The assignment of the structure of the products **11–16** was, in most cases, almost exclusively based on the comparison of their ^{1}H-n.m.r. data with those of structurally analogous glycosides[13–16] and was deduced from the magnitude of the H-4–H-5 coupling. For the structurally similar glycosides, a coupling constant $J_{4,5}$ ~3.5 Hz has been observed for the β-D series, whereas the corresponding α-D anomers have shown a constant $J_{4,5} \leqq 2$ Hz. Since, in the spectra of **11-16**, these couplings ranged from $J_{4,5}$ = 4.34 (**12**) to 3.54 Hz (**16**), all the compounds formed selectively possess the β-D configuration. By use of this analogy, only the structure of the minor product of the cyclopentenyl trimethylsilyl ether addition (isolated with **12**) remains somewhat uncertain, the coupling ($J_{4,5}$ 3.8 Hz) in



17

its spectrum is lower than that of **12**, but the value clearly is larger than those of α-D glycosides. Therefore, we corrected the assignment made earlier[10] and suggest that this side product belongs to the β-D series and has a configuration at C-2′ opposite to that of **12**. An additional support for the structural assignments of **11–17** can be

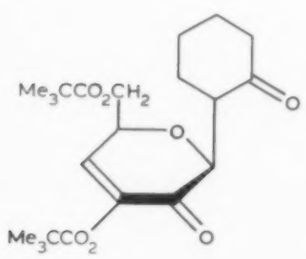


Scheme 1

drawn from the observation of Köll *et al.*[17] who found that the structurally similar *C*-α-D-glycosyl compounds having aromatic side chains at C-1 show a low coupling $J_{4,5} \leqq 2$ Hz.

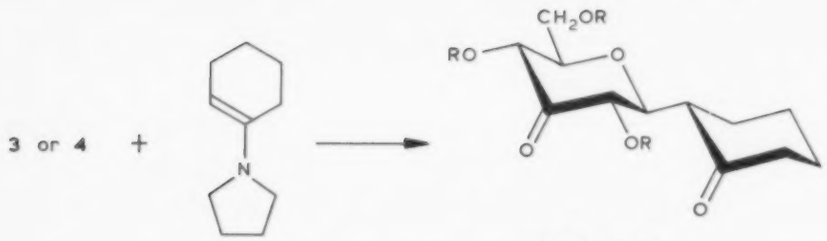
The larger H-4–H-5 coupling in the β-D series of these compounds has been explained in terms of a reduced dihedral angle between the bonds of H-4 and H-5, and consequently by a dominating ^1H_O(D) conformation[13–16], in which the large-size substituents have to take the quasi-axial orientation. For the *C*-glycosyl compounds **11–17**, this normally unfavored arrangement may be stabilized by intramolecular dipole interactions between the carbonyl oxygen atom in the side chain and the electrophilic ring-atoms C-2 and C-4.

The high stereocontrol of the *C*-glycosyl compound synthesis described herein may be explained in terms of a cyclic transition complex **A** (formulated for the formation of **11**) in which the C–C bond formation is assisted by a titanium-mediated interaction between the silyl group and the carbonyl oxygen atom. The approach of the silyl enol ether **5** from the upper (*Si*) side of the enulose **3** was obviously preferred, since the reactant approaching from below causes a steric repulsion with the 4-acetoxy substituent. The formation of the C–C bond was followed by an 2⟶3 acetyl shift, probably giving an orthoester-type intermediate **B** which, then, underwent an elimination of the 4-acetoxy substituent to form the *C*-glycosyl compound **11** (see Scheme 1). This accompanying rearrangement is hindered where the wandering acyl group is bulky. Consistent with this proposal, the pivaloyl-protected enulose **4** reacted with the trimethylsilyl enol ether **5** to give **18** in only 34% yield.



18

The suggestion outlined for the mechanism and the structural assignment for compounds **11–18** were both strongly supported by the results obtained in the Michael addition of 1-(1-cyclohexen-1-yl)pyrrolidine (**19**) to the enuloses **3** and **4**. In these reactions, compounds **20** and **21** having three newly created chiral centers at C-1,2, and 2′ were obtained. Here also, these reactions proceeded with high stereoselectivity. Among eight possible diastereomers, only one was formed. The structure of the 2-(2,4,6-tri-*O*-acyl-β-D-*ribo*-hexopyranosyl-3-ulose)cyclohexanones **20** and **21** was elucidated from the highfield ^{1}H-n.m.r. spectra, in which the doublets for H-4 and -2 occurred at δ 5.26 and 5.21 (**20**), and δ 5.23 and 5.18 (**21**), respectively. The



20 R = Ac
21 R = Me_3CCO

larger coupling constants $J_{4,5}$ 10.23 (**20**) and 10.55 Hz (**21**) reflected, in both cases, in the double triplets of H-5 proved the preferred $^4C_1$(D) conformation of these *C*-glycosyl compounds. Furthermore, the large coupling $J_{2,1}$ 10.88 Hz also observed in the signals of the anomeric protons at δ 4.37 (**20**) and 4.43 (**21**) is evidence for the β-D configuration of both compounds. All the assignments were confirmed by double-resonance experiments.

The high stereocontrol in the formation of **20** and **21** may be explained, once again, by the postulation of an intermediate, cyclic-transition complex **C** involving the orbital-controlled C–C bond formation and a cooperating interaction between the enamine nitrogen and the carbonyl carbon atoms (see Scheme 1). Model considerations revealed the favored enamine approach from the *Si*-site owing to the sterically hindered alternative *Re*-site reaction. Furthermore, in both C-glycosyl syntheses, the nonpolar ring members of the silyl enol ether **5** in **A**, as well as those of the enamine **19** in **C** would prefer the "*exo*" position producing the (*S*)-configuration at C-2′ of **11**, **12**, **20**, and **21**. The minor component, formed with **12** in the addition of the relatively planar cyclopentenyl derivative **6**, may have evolved from an "*endo*"-type transition complex corresponding to **A** and, therefore, would have the (*R*)-configuration at C-2′.

In conclusion, the Michael additions of trimethylsilyl enol ethers and of enamines to enuloses open up stereoselective routes to highly functionalized *C*-glycosyl compounds offering opportunities of broad structural variation.

EXPERIMENTAL

General methods. — Melting points are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. U.v. spectra were recorded with a Beckman Acta MVI spectrometer, and c.d. spectra with a JASCO J 41C spectral polarimeter. ^{1}H- and ^{13}C-n.m.r. spectra were recorded with (*a*) a Bruker WH-270 (270 MHz-^{1}H –, (*b*) a Bruker WH-90 (90 MHz-^{1}H and 22.63 MHz-^{13}C), or (*c*) a Bruker-AM-400 (400 MHz-^{1}H and 100.6 MHz-^{13}C) spectrometer with tetramethylsilane as the internal standard; the n.m.r. data are reported with arabic numbers for atoms of the residues and arabic numbers with prime for the carbon side-chain atoms. Mass spectra (m.s.) were registered with (*a*) a Varian MAT CH-7A (e.i.), (*b*) a

Varian MAT CH 711 (f.d.), or (*c*) a Finnigan MAT 312 (f.a.b.) spectrometer. Preparative l.c. under elevated pressure was performed with a Waters Prep 500 A equipped with cartouches (500 g silica 10–40), flash chromatography on silica MN 60 (0.04–0.063 mm, Macherey and Nagel), and t.l.c. on Silica gel GF_{254} (E. Merck, Darmstadt).

2,4,6-Tri-*O*-acetyl-1-deoxy-D-*erythro*-hex-1-enopyran-3-ulose (**3**) and 1-deoxy-2,4,6-tri-*O*-pivaloyl-D-*erythro*-hex-1-enopyran-3-ulose (**4**) were synthesized from 1,2,4,6-tetra-*O*-acetyl-β-D-glucopyranose (**1**) and 1,2,4,6-tetra-*O*-pivaloyl-β-D-glucopyranose (**2**) respectively, as described earlier[12]. Ligroin refers to the fraction of b.p. 45–70°.

*General procedure for the preparation of α-(3,6-di-*O*-acetyl-4-deoxy-β-*D*-glycero-hex-3-enopyranosyl-2-ulose)-carbonyl compounds* **11–16**. — To a solution of **3** (1 g, 3.5 mmol) in dry dichloromethane (10 mL) at −78° was added the corresponding trimethylsilyl enolether **5–10** (4.5 mmol) in dichloromethane (2 mL), followed by $TiCl_4$ (0.72 g, 3.8 mmol). In some reactions (as given in Table I), titanium tetra(2-propanolate) (0.38 mmol) and, after ~2 h, an additional amount of $TiCl_4$ (0.38 mmol) were added. The reaction was indicated by an intensive red or orange coloring of the solution. The mixture was stirred for the time given in Table I, and was then stopped by addition of 2M $KHCO_3$ solution (150 mL) and diethyl ether (80 mL). The aqueous phase was extracted twice with diethyl ether (80 mL), and the collected ether solutions were washed with water and with saturated $NaHCO_3$ solution (40 mL), dried (Na_2SO_4), and evaporated *in vacuo*. The remaining syrupy residue was purified by preparative l.c. under elevated pressure (1:1 ligroin–ethyl acetate). The yields are given in Table I.

*2-(3,6-Di-*O*-4-deoxy-β-*D*-glycero-hex-3-enopyranosyl-2-ulose)cyclohexanone* (**11**). — M.p. 89°, $[\alpha]_D^{22}$ 39.4° (*c* 1.4, chloroform); λ_{max}^{MeOH} 226 nm; c.d. (methanol): ε + 0.536 (λ = 335 nm); ^{1}H-n.m.r. (*a*, $CDCl_3$): δ 6.56 (d, 1 H, $J_{4,5}$ 4.25 Hz, H-4), 5.08 (d, 1 H, $J_{1,2}$ 2.40 Hz, H-1), 4.82 (ddd, 1 H, $J_{5,6a}$ 6.16, $J_{5,6b}$ 3.40 Hz, H-5), 4.71 (dd, 1 H, $J_{6a,6b}$ 12.0 Hz, H-6a), 4.26 (dd, 1 H, H-6b), and 3.03–3.00 (ddd, 1 H, $J_{2',1}$ 2.40, $J_{2',3'a}$ 7.38, $J_{2',3'b}$ 6.2 Hz, H-2′); ^{13}C-n.m.r. (*b*, C_6D_6): δ 206.5 (C-1′), 189.6 (C-2), 75.5 (C-1), 51.6 (C-2′), and 41.5 (C-6′).

Anal. Calc. for $C_{16}H_{20}O_7$ (324.3): C, 59.25; H, 6.21. Found: C, 58.97; H, 6.01.

*2′(S,R)-2-(3,6-Di-*O*-acetyl-4-deoxy-β-*D*-glycero-hex-3-enopyranosyl-2-ulose) cyclopentanones* (**12**). — The mixture of diastereomers **12** was obtained in 55% yield. The diastereomers were seperated by flash chromatography in 4:1 ligroin–acetone to give probably the 2*S* diastereomer as the main product (see Table I), oil, $[\alpha]_D^{22}$ +10.0° (*c* 0.78, chloroform), R_F 0.52 (2:1 ligroin–acetone); ^{1}H-n.m.r. (*a*, $CDCl_3$): δ 6.55 (d, 1 H, $J_{4,5}$ 4.37 Hz, H-4), 5.07 (d, 1 H, $J_{1,2'}$ 2.33 Hz, H-1), 4.78 (m, 1 H, H-5), 4.63 (dd, 1 H, $J_{6a,5}$ 5.88, $J_{6a,6b}$ 12.1 Hz, H-6a), 4.19 (dd, 1 H, $J_{6b,5}$ 3.40 Hz, H-6b), and 2.85 (m, 1 H, H-2′); ^{13}C-n.m.r. (*b*, $CDCl_3$): δ 217.6 (C-1′), 188.9 (C-2), 75.5 (C-1), 49.7 (C-2′), and 38.3 (C-5′); m.s (*a*): *m/z* 310 (M^+).

Anal. Calc. for $C_{15}H_{18}O_7$ (310.3): C, 57.97; H, 6.12. Found: C, 58.06; H,

5.85.

The minor product is probably the 2*R* diastereomer (yield 7%), oil, $[\alpha]_D^{22}$ −79° (*c* 0.86, chloroform), R_F (2:1 ligroin–acetone) 0.48; ^{1}H-n.m.r. (*b*, $CDCl_3$): δ 6.54 (d, 1 H, $J_{4,5}$ 3.81 Hz, H-4), 4.84 (d, 1 H, $J_{1,2'}$ 3.52 Hz, H-1), 4.82 (m, 1 H, H-5), 4.70 (dd, 1 H, $J_{6a,5}$ 5.28, $J_{6a,6b}$ 11.74 Hz, H-6a), 4.17 (dd, 1 H, $J_{6a,5}$ 2.93 Hz, H-6b), and 2.45 (m, 1 H, H-2′); ^{13}C-n.m.r. (*b*, $CDCl_3$): δ 216.0 (C-1′), 188.3 (C-2), 77.6 (C-1), 50.4 (C-2′), and 38.1 (C-5); m.s (*a*): *m/z* 310 (M^+).

Anal. Calc. for $C_{15}H_{18}O_7 \cdot 0.5\ H_2O$ (319.3): C, 56.42; H, 6.00. Found: C, 56.62; H, 6.14.

*2′-(3,6-Di-*O*-acetyl-4-deoxy-β-*D*-*glycero*-hex-3-enopyranosyl-2-ulose)acetophenone* (**13**). — The compound was purified by flash chromatochraphy in 4:1 ligroin–ethyl acetate, oil $[\alpha]_D^{22}$ −73° (*c* 1.3, chloroform), R_F (2:1 ligroin–ethyl acetone) 0.44; ^{1}H-n.m.r. (*a*, $CDCl_3$): δ 6.55 (d, 1 H, $J_{4'',5''}$ 3.80 Hz, H-4), 5.16 (dd, 1 H, $J_{1,2'a}$ 3.55, $J_{1,2'b}$ 7.33 Hz, H-1), 4.82 (m, 1 H, H-5), 4.63 (dd, 1 H, $J_{6a,5}$ 6.08, $J_{6a,6b}$ 12.07 Hz, H-6a), 4.20 (dd, 1 H, $J_{6b,5}$ 3.51 Hz, H-6b), 3.55 (dd, 1 H, $J_{2'a,2'b}$ 17.34 Hz, H-2′a), and 3.41 (dd, 1 H, H-2′b); ^{13}C-n.m.r. (*b*, $CDCl_3$): δ 197.8 (C-1′), 190.7 (C-2), 137.9 (ipso-C), 75.5 (C-1), and 40.3 [C-2 (ω)]

Anal. Calc. for $C_{18}H_{18}O_7$ (346.3): C, 62.42; H, 5.24. Found: C, 62.49; H, 5.29.

*(3,6-Di-*O*-acetyl-4-deoxy-β-*D*-*glycero*-hex-3-enopyranosyl-2-ulose)propanone* (**14**). — The product crystallized from diethyl ether, m.p. 65°, $[\alpha]_D^{22}$ −98° (*c* 1.2, chloroform), ^{1}H-n.m.r. (*a*, $CDCl_3$): δ 6.52 (d, 1 H, $J_{4,5}$ 3.88 Hz, H-4), 4.94 (dd, 1 H, $J_{1',1'a}$ 4.08, $J_{1,1'b}$ 7.43 Hz, H-1), 4.77 (m, 1 H, H-5), 4.59 (dd, 1 H, $J_{6a,5}$ 6.18, $J_{6a,6b}$ 12.04 Hz, H-6a), 4.17 (dd, 1 H, $J_{6b,5}$ 3.55 Hz, H-6b), 2.97 (dd, $J_{1'a,1'b}$, 17.07 Hz, H-1′a), and 2.84 (dd, 1 H, H-1′b); ^{13}C-n.m.r. (*b*, $CDCl_3$): δ 204.1 (C-2′), 188.6 (C-2), 74.1 (C-1), and 44.0 (C-1′); m.s. (f.a.b.;*c*): *m/z* 285 ($M^+ + 1$).

Anal. Calc. for $C_{13}H_{16}O_7$ (284.3): C, 54.93; H, 5.67. Found: C, 55.19; H, 5.60.

*2′-(3,6-di-*O*-acetyl-4-deoxy-β-*D*-*glycero*-hex-3-enopyranosyl-2-ulose)isobutyraldehyde* (**15**). — The compound was purified by flash chromatography in 5:2 ligroin–ethyl acetate, oil, $[\alpha]_D^{22}$ −110° (*c* 1.4, chloroform), R_F (1:1 ligroin–ethyl acetate) 0.52; ^{1}H-n.m.r. (*b,c*; CD_2Cl_2): δ 9.54 (s, 1 H, CHO), 6.60 (d, 1 H, $J_{4,5}$ 4.12 Hz, H-4), 4.87 (m, 1 H, H-5), 4.71 (s, 1 H, H-1), 4.68 (dd, 1 H, $J_{6a,5}$ 7.19, $J_{6a,6b}$ 12.24 Hz, H-6a), 4.11 (dd, 1 H, $J_{6b,5}$ 3.49 Hz, H-6b), and 1.12 (s, 6 H, CH_3–C); ^{13}C-n.m.r. (*c*, CH_2Cl_2): δ 202.1 (CHO), 188.9 (C-2), 80.5 (C-1), and 50.2 (C-2′); m.s (f.d.; *b*): *m/z* 299 ($M^+ + 1$, base peak). The product contains small amounts of impurities; therefore, it was transformed into its trimethylene dithioacetal **17**.

tert-*Butyl 2-(3,6-Di-*O*-acetyl-4-deoxy-β-*D*-*glycero*-hex-3-enopyranosyl-2-ulose)acetate* (**16**). — The crude product was purified by flash chromatography in 3:1 ligroin–ethyl acetate, oil $[\alpha]_D^{22}$ −30.1° (*c* 1.6, chloroform), R_F (1:1 ligroin–ethyl acetate) 0.53; ^{1}H-n.m.r. (*a*, $CDCl_3$): δ 6.52 (d, 1 H, $J_{4,5}$ 3.54 Hz, H-4), 4.9–4.8 (m, 2 H, H-5,1), 4.55 (dd, 1 H, $J_{6a,5'}$ 5.92, $J_{6a,6b}$ 12.03 Hz, H-6a), 4.18 (dd, $J_{6b,5}$ 3.62 Hz, H-6b), 2.82 (dd, 1 H, $J_{2'a,1}$ 4.07, $J_{2'a,2'b}$ 17.08 Hz, H-2′a), and

2.69 (dd, 1 H, $J_{2'b,1}$ 7.44 Hz, H-2'b).

Anal. Calc. for $C_{16}H_{22}O_8 \cdot 0.5\ H_2O$ (351.3): C, 54.69; H, 6.60. Found: C, 54.34; H, 6.83.

*2-[2-(3,6-Di-O-acetyl-4-deoxy-β-*D*-glycero-hex-3-enopyranosyl-2-ulose)-2-propyl]-1,3-dithiane* (**17**). — To a solution of the crude **15** (obtained from 1.75 mmol of **3**) in chloroform (10 mL) was added propane-1,3-dithiol (0.23 g, 2.1 mmol). The mixture was stirred for 3 h at room temperature and then evaporated *in vacuo*. The remaining residue was purified by flash chromatography in 5:2 ligroin–ethyl acetate to give **17** (0.42 g, 62%), pale yellow oil, $[\alpha]_D^{22}$ +69.7° (*c* 1.6, chloroform), R_F (1:1 ligroin–acetate) 0.59; ^{1}H-n.m.r. (*c*, $CDCl_3$): δ 6.45 (d, 1 H, $J_{4,5}$ 4.28 Hz, H-4), 4.82 (m, 1 H, H-5), 4.66 (s, 1 H, H-1), 4.58 (s, 1 H, H-2 dithiane), 4.51 (dd, 1 H, $J_{6a,5}$ 6.41, $J_{6a,6b}$ 12.04 Hz, H-6a), 4.19 (dd, 1 H, $J_{6b,5}$ 3.61 Hz, H-6b), 3.0–2.8 (m, 4 H and H-6 dithiane), 1.20 and 1.14 [2 s, 6 H, $(CH_3)_2C$]; ^{13}C-n.m.r. (*c*, $CDCl_3$): δ 189.0 (C-2), 79.4 (C-1), 58.4 (C-2 dithiane), and 43.5 (Me_2C); m.s (*a*): *m/z* 388 (M^+).

Anal. Calc. for $C_{17}H_{26}O_6S_2$ (388.5): C, 52.56; H, 6.23. Found: C, 52.36; H, 6.16.

*2-(3,6-Di-O-pivaloyl-4-deoxy-β-*D*-glycero-hex-3-enopyranosyl-2-ulose) cyclohexanone* (**18**). — To a solution of **4** (0.5 g, 1.21 mmol) and cyclohexenyl trimethylsilyl ether **5** (0.3 g, 1.8 mmol) in dry dichloromethane (10 mL), at −78° was added $TiCl_4$ (0.34 g, 1.8 mmol). The intensively red-colored solution was stirred for 30 min at −78°. The reaction was stopped by the addition of Na_2CO_2) (0.5 g) in water (10 mL). The mixture was processed as described for **11** to give a syrupy product (320 mg) containing a main product, R_F 0.57 (3:1 ligroin–ethyl acetate) and some side products. Preparative l.c. in 6:1 ligroin–ethyl acetate yielded **18** (0.17 g, 34%), colorless oil, $[\alpha]_D^{22}$ −47° (*c* 1.1, chloroform); ^{1}H-n.m.r. (*a*, $CDCl_3$): δ 6.47 (d, 1 H, $J_{4,5}$ 3.97 Hz, H-4), 5.14 (d, 1 H, $J_{1,2'}$ 2.55 Hz, H-1), 4.84 (m, 1 H, H-5), 4.60 (dd, 1 H, $J_{6a,5}$ 5.5, $J_{6a,6b}$ 12.0 Hz, H-6a), and 4.07 (dd, 1 H, $J_{6b,5}$ 3.6 Hz, H-6b).

Anal. Calc. for $C_{22}H_{32}O_7 \cdot H_2O$ (426.5): C, 61.95; H, 8.04. Found: C, 62.24; H, 8.50.

*2-(2,4,6-Tri-O-acetyl-β-*D*-ribo-hexopyranosyl-3-ulose)cyclohexanone* (**20**). — A solution of **3** (0.5 g, 1.74 mmol) and 1-(1-cyclohexen-1-yl)pyrrolidine (**19**; 0.28 g, 1.8 mmol) in 1,4-dioxane (7 mL) was stirred at room temp. for 2 days. The mixture was poured into ice (20 g) and aqueous HCl (20 mL). The mixture was extracted five times with diethyl ether (30 mL). The ether solution was washed with sat. $NaHCO_3$ solution (30 mL) and with water, dried (Na_2SO_4), and evaporated *in vacuo*. As monitored by t.l.c. (1:2 ligroin–ethyl acetate), the syrupy residue (0.33 g, 49%) contained only one main product (R_F 0.62) and traces of nonpolar impurities. It was purified by column chromatography on silica (180 g; 1:2 ligroin–ethyl acetate to give **21** (0.13 g, 20%), colorless oil, $[\alpha]_{578}^{22}$ −1.4°, $[\alpha]_{546}^{22}$ −0.9°, $[\alpha]_{436}^{22}$ +5.9°, $[\alpha]_{365}^{22}$ +5.8° (*c* 1.2, chloroform), ^{1}H-n.m.r. ($CDCl_3$): δ 5.26 (d, 1 H, $J_{4,5}$ 10.55 Hz, H-4), 5.21 (d, 1 H, $J_{1,2'}$ 10.88 Hz, H-2), 4.37 (dd, 1 H, $J_{1,2'}$ 1.98, H-1), 4.28 (d, 2 H, $J_{6,5}$ 3.5 Hz, H-6), and 3.93 (dt, 1 H, H-5); f.d.m.s. (*c*): *m/z* 384 (100%, M^+) and 385

(74%, $M^+ + 1$).

Anal. Calc. for $C_{18}H_{24}O_9 \cdot H_2O$ (402.4): C, 53.72; H, 6.51. Found: C, 53.82; H, 6.04.

*2-(2,4,6-Tri-O-pivaloyl-β-*D-ribo-*hexopyranosyl-3-ulose)cyclohexanone* (**21**). — This compound was obtained from **4** (0.5 g, 1.21 mmol) and **19** (0.2 g) in 1,4-dioxane (7 mL) in a manner analogous to the preparation of **20**. T.l.c. (3:1 ligroin–ethyl acetate) of the crude product indicated a main (R_F 0.75) and a minor component (R_F 0.18). By column chromatography on silica (250 g; 6:1 ligroin–ethyl acetate), **21** (170 mg, 28%) was isolated as a colorless oil, which crystallized during drying *in vacuo*, m.p. 145–146°, $[\alpha]_D^{22}$ +31.8° (*c* 1.5, chloroform); ^{1}H-n.m.r. (*a*, $CDCl_3$): δ 5.23 (d, 1 H, $J_{4,5}$ 10.23 Hz, H-4), 5.18 (d, 1 H, $J_{2,1'}$ 10.88 Hz, H-2), 4.43 (dd, 1 H, $J_{1,2'}$ 2.0 Hz, H-1), 4.33 (dd, 1 H, $J_{6a,5}$ 2.3, $J_{6a,6b}$ 12.2 Hz, H-6a), 4.20 (dd, 1 H, $J_{6b,5}$ 4.62 Hz, H-6b), and 3.90 (ddd, 1 H, H-5); f.d.m.s. (*c*): 510 (75%, M^+) and 511 (19%, $M^+ + 1$).

Anal. Calc. for $C_{27}H_{42}O_9$ (510.6): C, 63.40; H, 8.36. Found: C, 63.53; H, 8.23.

ACKNOWLEDGMENTS

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SYNTHESIS AND "ANOMERIZATION" OF *C*-GLYCOSYL COMPOUNDS RELATED TO SOME HETEROCYCLIC NATURAL PRODUCTS*

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ABSTRACT

Reaction of 2,3-*O*-isopropylidene-D-ribofuranose (**13**) with the stabilized Wittig reagents $Ph_3P{=}C(Me)CO_2Me$ (**14**) and $Ph_3P{=}C(Me)CN$ (**15**) gave olefinic products which, upon treatment with dilute base, afforded the corresponding anhydro sugars having the β-D-anomer configuration exclusively. Treatment of these kinetic products with a strong base did not affect the ester obtained from **14**, but the nitrile from **15** gave a β-to-α-anomer ratio at equilibrium of 4:1. Reaction of **13** with $Ph_3P{=}CHCOMe$ led directly to a 7:3 mixture of β- and α-D anomers, and this ratio was changed to 1:4 upon prolonged exposure to base. Treatment of 4,6-*O*-ethylidene-D-glucopyranose with the Wittig reagent $Ph_3P{=}CHCOCH_2CO_2Et$ led directly to a 1:1 mixture of the anomers of the anhydro sugar in which a β-keto ester residue is attached at the (original) anomeric center. This ratio of anomeric forms could not be changed by treatment with base, but the ethylidene-protecting group could be removed, and the resulting tetrol tritylated at the primary position.

INTRODUCTION

The *C*-glycosyl monosaccharides are derivatives of tetrahydrofurans or tetrahydropyrans, heterocyclic ring systems that are also encountered frequently in a wide variety of natural products. These natural products may, therefore, be regarded as elaborate *C*-glycosyl compounds and, hence, carbohydrate-based approaches to their syntheses seem justified. Nonactic acid[1] (**1**) and trichothecanes, such as **2** (ref. 2) are two such natural products, and we have been interested in adapting the methods of synthesis of *C*-glycosyl compounds to their preparation.

*Taken, in part, from the Ph.D. thesis of King Mo Sun, University of Maryland, 1981, and Robert D. Dave, University of Waterloo, 1982.

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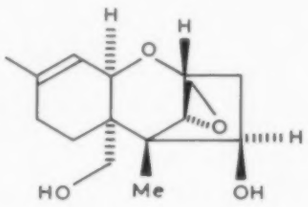
Preliminary communications related to these objectives have appeared[3,4] and, in this report, we describe some support studies which are of general interest.

From the standpoint of *C*-glycosyl chemistry, the synthetic challenge for target compounds **1** or **2** is the local element of symmetry about the heterocyclic ring. Thus, if nonactic acid is represented as **3**, the local element of symmetry is seen to be a mirror plane (**A**) which bisects the molecule, whereas for the trichothecane **4**, there is a C_2 axis represented by **B**.

For a given heterocyclic ring system, equilibration of **3** and **4** is theoretically possible provided that appropriate functional elements are present, and this permits a considerable degree of flexibility in synthetic planning.

1



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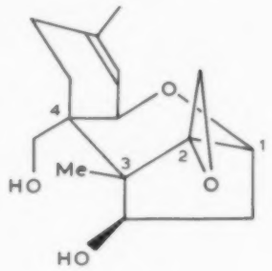
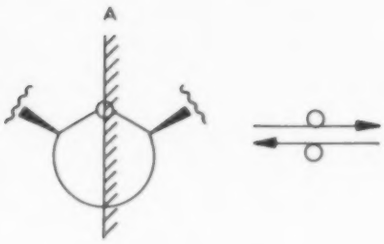


$^4C_1$ (D)

2a



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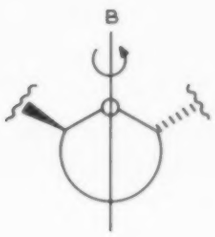

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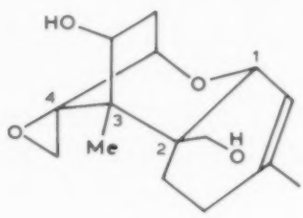
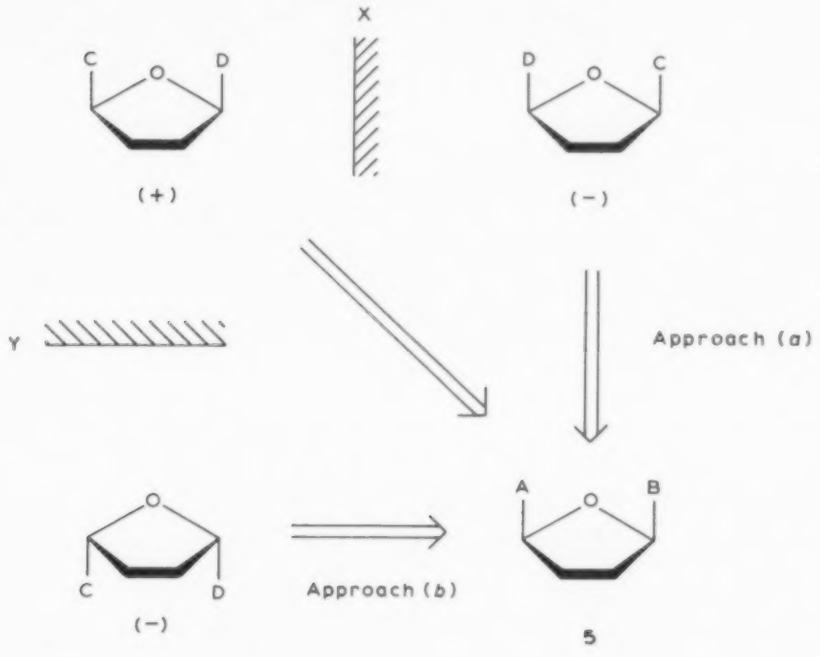


$^1C_4$ (D)

2b

The possible interconversion of **3** and **4** is particularly relevant in the case of nonactic acid (**1**) since, in the macrotetrolide nonactin, both enantiomers occur in alternating sequence, as a result of which the macrocycle exhibits an S_4 symmetry and is optically inactive[5]. Ideally, the need for equal amounts of each enantiomer could be met by an enantiodivergent procedure in which the enantiomeric forms of **1** are derived from a single precursor. The considerations of symmetry in connection with **3** and **4** individually, and the ability to convert **3** into **4** (or vice versa), suggested two approaches to nonactic acid (see Scheme 1), which differ according to the mirror plane that is used to reflect the crucial key intermediate, represented as **5**. Thus, approach (*a*) utilizes the mirror plane **X** and would require the transformation of the functional groups, **A** and **B** into **C** and **D**, respectively, to give one enantiomer [designated arbitrarily as (+)], and into **D** and **C**, respectively, to give the (−) enantiomer. In approach (*b*), the mirror plane **Y** is used and the (+) enantiomer is obtained as mentioned before; however, the (−) enantiomer is now obtained by a double epimerization of the side chains.

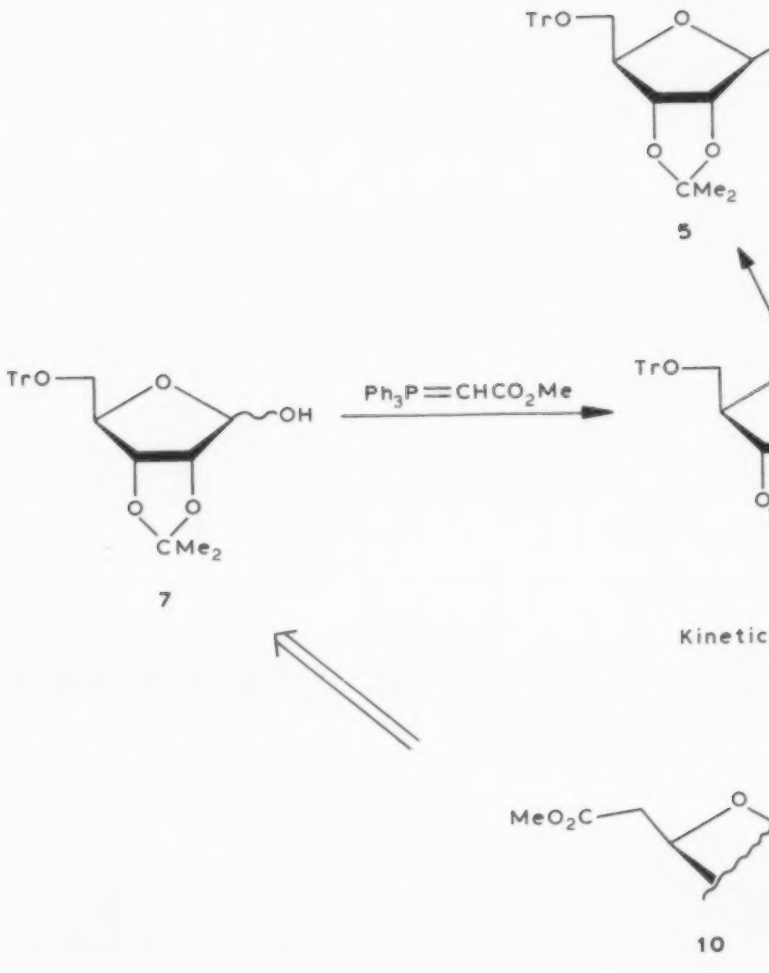
The first prerequisite for probing the application of this general plan was to



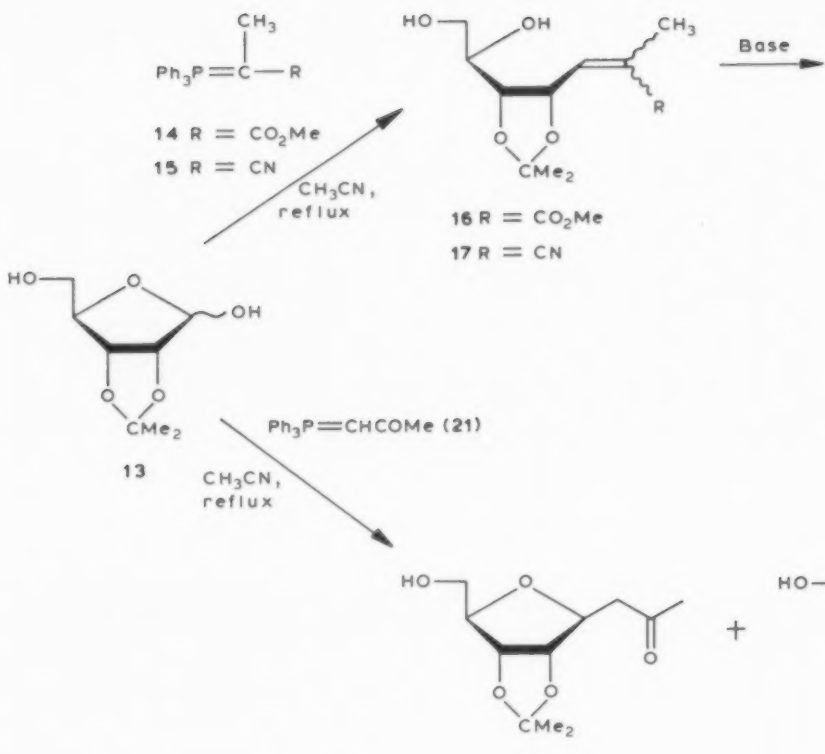
Scheme 1.

establish the feasibility of the proposed "anomerizations". Of particular significance, in this regard, was the detailed study reported by Ohuri *et al.*[6] who had shown that the isomers **8** and **9** could be obtained as kinetic and thermodynamic products, respectively, of Wittig reactions of 2,3-*O*-isopropylidene-5-*O*-triphenylmethyl-D-ribofuranose (**7**). Indeed, **8** seemed an ideal precursor for our work, since Chu *et al.*[7] had reported the formation of the salt **5**, which indicated that a one-carbon unit could be attached to the activated methylene group of the side chain. These results seemed promising for approach (*a*) (Scheme 1), since the primary hydroxyl group of **7** would provide a ready access to ester **10**, to which the Chu *et al.* method[7] could be applied for the synthesis of the salt **11** from which the derivative **12** would be prepared. This approach was abandoned, however, when we found it impossible to obtain the methyl ester **6**, either from salt **5** or by direct alkylation of **8**.

In an alternative approach, 2,3-isopropylidene-D-ribofuranose[8] (**13**) was treated with the stabilized Wittig reagent (2-methoxycarbonylethylidene)triphenylphosphorane (**14**) in refluxing acetonitrile for 4 h to afford an isolable intermediate, presumed to be the (*E,Z*) mixture **16** in 95% yield. Brief treatment with dilute base gave a mixture of two compounds (in 3:1 ratio) which could be separated by column chromatography. Their structures as epimers of the β-D anomer **18** were established by their transformation into nonactic acid (**1**) and its 2-epimer[3]. Reaction of **13** with (2-cyanoethylidene)triphenylphosphorane (**15**) also gave an excellent yield of an isolable alkene **17**, which cyclized readily to give the anhydro sugar **19**. The reaction of **13** with acetonylidenetriphenylphosphorane (**21**), in acetonitrile at reflux for 2 h, led to the anomers **22** and **23** in the ratio 7:3 without any evidence for an unsaturated intermediate.


TrO
O
O
O
CMe2
5
TrO
O
OH
O
O
CMe2
7
Ph3P=CHCO2Me
TrO
O
Kinetic
MeO2C
O
10

ONa
CO2Me
TrO
CH3
CO2Me
CMe2
6
CO2Me
CMe2
8
TrO
CO2Me
CMe2
9
Thermodynamic product
NaO
MeO2C
MeO2C
11
12



Kinetic ratio	7
Thermodynamic ratio (10 mM methanol)	1

18 R = CO_2Me
19 R = CN

20

+ 19 (20%)

24

23

3

4

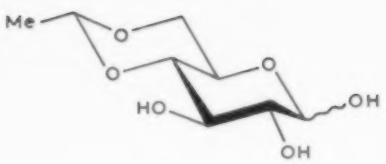
In light of the results from Moffatt's laboratory[6], the (major) products of kinetic control should be the α anomers, and the preliminary assignments of the (major) reaction products **18, 19,** and **22** were made on this basis. Accordingly, prolonged treatment with base should effect equilibration, yielding the corresponding α anomers as the major products of thermodynamic control[6]. The availability of both anomers in each case would greatly facilitate the structural proof by the ^{13}C-n.m.r. techniques pioneered by Moffatt and associates[6] (*vide infra*).

In the case of **22** and **23**, the ratio (7:3) in which they were formed, could be changed to 1:4 by treating the mixture with 10mM sodium methoxide in methanol for 30 min. However, in the case of the ester **18**, treatment with 10mM methanolic sodium methoxide solution at room temperature for 16 h had no effect (t.l.c. and ^{1}H-n.m.r.), and even the drastic conditions of 0.3M methanolic sodium methoxide solution at reflux for 10 h failed to offer any formation of **20**. On the other hand, treatment of the nitrile **19** with 0.3M ethanolic sodium ethoxide solution at reflux for 4 h caused anomerization to afford a 4:1 mixture of **24** and **19**. The α anomers **24** could be separated from the β anomer **19**; however, separation of the epimers of each anomer was not achieved.

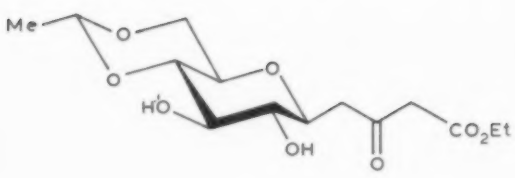
The aforementioned results indicated that the α and β anomers could be readily obtained in the case of the nitrile (**19** and **24**) and propanone derivatives (**22** and **23**), but not in the case of the ester **18**, thus delineating the possible choices of functional groups that could be utilized for the double epimerization outlined in approach (*b*) (Scheme 1). Thus, residue **D** could be $-CH(CH_3)CN$, but not $-CH(CH_3)CO_2R$, and residue **C** could be $-CH_2COMe$. This information was used for the final synthesis[3].

With respect to the trichothecene system **2**, the procedure to be adopted for a carbohydrate-based approach would depend on whether the molecule is represented in the $^4C_1$(D) (**2a**), or $^1C_4$(D) conformation (**2b**), and these considerations have been discussed elsewhere[4]. However, in either case, a *C*-α-D-glycopyranosyl derivative is needed that would provide access to an "annulated pyranose" having a bridged structure (**2a**) or a fused system (**2b**). A β-keto ester seemed to be an interesting candidate for these objectives.

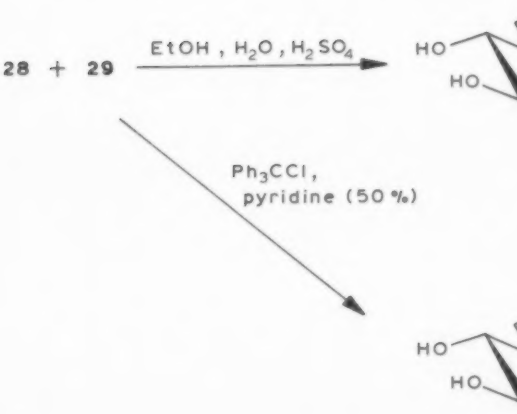
Reaction of (ethoxycarbonylacetonylidene)triphenylphosphorane (**26**) with 4,6-*O*-ethylidene-D-glucopyranose[9] (**25**) in refluxing acetonitrile gave the expected *C*-glucopyranosyl compounds **28** and **29** without any evidence of intermediate **27**. Because of difficulties in removing triphenylphosphine oxide, only very small amounts of the pure products could be isolated, even after repeated, careful chromatography. However, t.l.c. indicated that the two components were present in approximately equal amounts. The optical rotation was +34.6° for the fastest-moving anomer (R_F 0.65) and −28.7° for the more polar (R_F 0.61). Since Hudson's rule of isorotation has been shown to be valid for *C*-glucopyranosyl compounds[10], the structures **28** and **29** were assigned to the α-D and β-D anomer, respectively. Support for these conclusions was provided by the ^{1}H-n.m.r. (600 MHz) spectra which, in the case of the β anomer **29** was easily interpreted. However, for the α


Me
O
O
O
HO
OH
OH
Ph3P=CHCO

25


Me
O
O
O
HO
OH
CO2Et
O

28


28 + 29
EtOH , H2O , H2SO4
HO
HO
Ph3CCl,
pyridine (50 %)
HO
HO

27

29

30

31

32

33

anomer **28** the spectrum was exceedingly complex, a result which was ascribed to the presence of the hemicetal form **30** to an appreciable extent.

In view of the aforementioned difficulties with isolation, we found it best to treat the crude product from the Wittig reaction with acidic aqueous ethanol, the water being present to reduce the possibility of forming a mixed acetal from the α anomer **28**. The resulting tetrols (**31** and **32**) were readily separated from triphenylphosphine oxide by extraction into water. Evaporation of the aqueous phase and column chromatography of the residue afforded both compounds as oils, which gave acceptable elemental analyses. The optical rotations of +5.7 and +9.1° were consistent with the assignments of structures **31** and **32**, respectively. The high polarity of these tetrols presented a problem for further synthetic studies in view of their insolubility in organic solvents. This was overcome by tritylation, but the resulting compound **33**, indeed soluble in organic solvents, was obtained in a disappointingly low yield.

The stereoselectivity in the formation of **28** and **29** was low and, unlike in the case of **22** and **23**, the ratio in which they were formed could not be altered by equilibration, as the most acidic protons are undoubtedly the activated methylene group. Hence, retrocyclization of the pyrano ring is unlikely. Indeed, **28** and **29** were unchanged by prolonged treatment with sodium methoxide, and attempts to force the reaction led to decomposition.

The results obtained with the furanose system indicated the functional groups that could be used for the "anomerizations" required in approach (*b*) (Scheme 1), which led to the final synthesis of methyl (+)- and (−)-nonactates[3]. However, in the case of the pyranose system, the β-keto ester derivatives were not suitable as chirons[11] for trichothecenes, since it was not possible to increase the ratio of the desired α anomers. Therefore, an alternative procedure was adopted for the synthesis of the trichothecane skeleton[4].

EXPERIMENTAL

General methods. — Melting points were determined in capillary tubes with a Büchi 510 melting-point apparatus, and are uncorrected. Optical rotations were determined with a Perkin–Elmer 241 polarimeter. I.r. spectra were recorded with a Perkin–Elmer IR-298 spectrometer using NaCl cells and chloroform as solvent for solids or sodium chloride plates for films. ^{1}H-N.m.r. spectra were recorded with Varian EM-360A (60 MHz), Bruker WP-80 (80 MHz), Varian XL-100 (100 MHz), Varian HR-220 (220 MHz) spectrometers and a 600-MHz spectrometer on solutions in $CDCl_3$ (internal Me_4Si); coupling constants were obtained by measuring the spacings of the spectra judged to be first order. The progress of all reactions was monitored by t.l.c. on Silica gel 60 (HF-254, Merck) using the following solvent systems: ethyl acetate–light petroleum ether (*A* 1:4), dichloromethane–methanol (*B* 4:1, *C* 9:1, *D* 19:1, *E* 24:1, *F* 1:9, and *G* 1:4), and diethyl ether (*H*). The chromatograms were viewed under u.v. light and charred with

H_2SO_4. Flash column chromatography was performed in Kieselgel 60 (230–400 mesh, Merck). Elemental analyses were performed by Dr. F. Kasler (Department of Chemistry, University of Maryland) or by Guelph Chemical Laboratories (Guelph, Ontario, Canada).

Standard procedure for the reaction of furanose with stabilized Wittig reagents. — The furanose (1 equiv.) and Wittig reagent (1.5 equiv.) were dissolved in dry acetonitrile (1 g of sugar/50 mL). The solution was boiled under reflux and, when the reaction was complete (t.l.c.), the solvent was evaporated and the residue chromatographed.

*Reaction of 2,3-*O*-isopropylidene-*D*-ribofuranose* (**13**) *with (2-methoxycarbonylethylidene)triphenylphosphorane* (**13**) *and cyclization of the intermediate* **16** *into methyl 3,6-anhydro-2-deoxy-4,5-*O*-isopropylidene-2-*C*-methyl-*D*-glycero-*D*-allo- and -*D*-altro-heptonate* (**18**). — Under the standard Wittig reaction conditions, **13** (ref. 8) (250 mg, 1.32 mmol) and **16** (700 mg, 2 mmol) reacted to give **16** (325 mg, 95%), R_F 0.44 (*H*); $\nu_{max}^{CHCl_3}$ 3480 (OH), 1715, and 1662 (α,β-unsaturated ester) cm^{-1}; ^{1}H-n.m.r. (60 MHz): δ 1.44 (s, 6 H, $OCMe_2$), 1.95 (d, 3 H, H_3-8), 2.90–3.43 (br.s, 2 H, 2 OH), 3.68–4.01 (m, 7 H, H-5,6,7a,7b, CO_2CH_3), 4.00–4.87 (dd, 1 H, $J_{3,4}$ 9.0, $J_{4,5}$ 6.0 Hz, H-4), and 6.66 (dd, 1 H, $J_{3,8}$ 0.7 Hz, H-3).

Anal. (h.r.m.s.): Calc. for $C_{11}H_{17}O_6$ ($M^+ - CH_3$): 245.1025. Found: 245.1043.

To a solution of **16** (130 mg, 0.5 mmol) in 1,4-dioxane, was added 2% methanolic KOH solution (1 mL). The mixture was stirred for 5 min at room temperature and then made neutral with 1% HCl. After removal of solvent under reduced pressure, the residue showed two components (t.l.c., *H*) which were separated by chromatography.

First component (31 mg, 24%): R_F 0.43 (*H*), $[\alpha]_D^{20}$ +10.9° (*c* 2.63, chloroform); $\nu_{max}^{CHCl_3}$ 3500 (OH) and 1730 (ester) cm^{-1}; ^{1}H-n.m.r. (220 MHz): δ 1.28 (d, 3 H, $J_{2,8}$ 7.0 Hz, H_3-8), 1.35 (s, 3 H, $OCCH_3$), 1.57 (s, 3 H, $OCCH_3$), 2.55 (br.s, 1 H, OH), 2.81 (quint., 1 H, $J_{2,3}$ 7.0 Hz, H-2), 3.67 (s, 3 H, CO_2CH_3), 3.25–3.83 (m, 2 H, H_2-7), 4.00 (m, 2 H, H-3,6), 4.65 (dd, 1 H, $J_{3,4}$ 3.8, $J_{4,5}$ 6.5 Hz, H-4), and 4.71 (dd, 1 H, $J_{5,6}$ 3.8 Hz, H-5); m.s.: *m/z* 245 ($M^+ - CH_3$), 229 ($M^+ - OCH_3$), and 213 ($M^+ - CH_3O_2$).

Second component (97 mg, 75%): R_F 0.38 (*H*), $[\alpha]_D^{20}$ −11.1° (*c* 0.90, chloroform); $\nu_{max}^{CHCl_3}$ 3470 (OH) and 1730 cm^{-1} (ester); ^{1}H-n.m.r. (220 MHz): δ 1.28 (d, 3 H, H_3-8), 1.38 (s, 3 H, $OCCH_3$), 1.57 (s, 3 H, $OCCH_3$), 2.68 (quint., 1 H, $J_{2,3}$ 7.0, $J_{2,8}$ 7.0 Hz, H-2), 3.10 (br.s, 1 H, OH), 3.77 (s, 3 H, CO_2CH_3), 3.61–3.89 (m, 2 H, H_2-7), 4.00–4.16 (m, 2 H, H-3,6), 4.51 (dd, 1 H, $J_{3,4}$ 4.2, $J_{4,5}$ 6.8 Hz, H-4), and 4.75 (dd, 1 H, $J_{5,6}$ 3.5 Hz, H-5).

Anal. (h.r.m.s.): Calc. for $C_{11}H_{17}O_6$ ($M^+ - CH_3$) 245.1025. Found: 245.1039.

(2-Cyanoethylidene)triphenylphosphorane (**15**). — A three-necked, 2-L, round-bottom flask, equipped with a condenser was charged with 2-hydroxypropanenitrile (100 g, 1.4 mol), dry pyridine (110 mL, 1.4 mol), and anhydrous diethyl ether (1 L). Thionyl chloride (83 g, 0.7 mol) was added slowly to the

ethereal solution over 0.5 h and, after being stirred for another 0.5 h, the solution was filtered under vacuum into a 2-L, 2-necked, round-bottom flask equipped with a condenser and drying tube. Thionyl bromide was added and the solution was boiled under reflux for 24 h, cooled, transferred to a dropping funnel, and added carefully to a vigorously stirred suspension of excess anhydrous $NaHCO_3$ in dry diethyl ether, at such a rate controlled evolution of CO_2 took place. After the addition was complete, the mixture was filtered, the solids were washed with diethyl ether (200 mL), and the filtrate was evaporated to dryness. The deep-red, crude product was distilled under vacuum (58–60°, 3.3 kPa) to give 2-bromopropanenitrile (46 g) as a colorless liquid. A portion (20 g, 0.15 mmol) of this material and triphenylphosphine (40 g, 0.15 mmol) were dissolved in dry toluene (200 mL) and the solution was refluxed for 12 h. The white solid formed was collected, washed well with anhydrous diethyl ether (3 × 50 mL) (55 g, 91.7%), recrystallized from dichloromethane–diethyl ether. To a solution of this salt (25 g, 63 mmol), in dry dichloromethane (250 mL), was added finely powdered anhydrous K_2CO_3 (20 g, 145 mmol) and the suspension was stirred vigorously for 4 h at room temperature. The solids were collected by filtration and washed with dry dichloromethane (3 × 50 mL). The filtrate and the washings were combined and the solvent was removed to give a yellow solid (19.9 g, 100%) which crystallized from diethyl ether–petroleum ether (30–60°), m.p. 168–169°; ^{1}H-n.m.r. (60 MHz): δ 1.72 (d, 3, J_{P,CH_3} 17.6 Hz, CH_3) and 7.2–8.05 [m, 15 H, J_{P,CH_3} $P(C_6H_5)_3$].

Anal. Calc. for $C_{21}H_{18}NP$: C, 80.00; H, 5.71; N, 4.40. Found: C, 79.60; H, 5.74; N, 4.32.

Reaction of **13** *with* **15** *and cyclization of the intermediate* **17** *into 3,6-anhydro-2-deoxy-4,5-*O*-isopropylidene-2-C-methyl-*D-glycero-D-allo- *and* -D-altro-*heptononitrile* (**19**). — Reaction of **15** (1.2 g, 6.3 mmol) with **13** (3 g, 9.5 mmol) under the standard Wittig reaction procedure afforded **17**, R_F 0.27 (*H*); $\nu_{max}^{CHCl_3}$ 3420 (OH), 2215 (CN), and 1650 cm^{-1} (double bond); ^{1}H-n.m.r. (60 MHz): δ 1.40 (s, 3 H, OCC*H*$_3$), 1.50 (s, 3 H, OCC*H*$_3$), 2.00 (d, 3 H, $J_{3,8}$ 1.0 Hz, H_3-8), 3.48–3.91 (m, 5 H, H-5,7a,7b, 2 OH), 4.00–4.29 (m, 1 H, H-6), 4.86–5.10 (dd, 1 H, $J_{3,4}$ 5.5, $J_{4,5}$ 5.5 Hz, H-4), and 6.25–6.35 (dd, 1 H, H-3). A portion of **17** (500 mg, 2.2 mmol) was dissolved in methanol (25 mL) and a catalytic amount of sodium methoxide added. After stirring for 20 min at 25°, the reaction was quenched by addition of 1% methanolic HCl, the solvent evaporated, and the residue passed through a short chromatographic column. The product (500 mg, 100%) thus obtained was homogeneous on t.l.c. (*H*), but was shown to be a mixture of two compounds by ^{1}H-n.m.r., R_F 0.49 (*H*), 0.43 (*E*); $\nu_{max}^{CHCl_3}$ 3500 (OH) and 2253 cm^{-1} (CN).

First component: ^{1}H-n.m.r. (220 MHz): δ 1.39 (s, 3 H, OCC*H*$_3$), 1.40 (d, 3 H, $J_{2,8}$ 7.5 Hz, H_3-8), 1.57 (s, 3 H, $OCCH_3$), 2.72 (br.s, 1 H, OH), 3.12 (dq, 1 H, $J_{2,3}$ 5.5, $J_{2,8}$ 7.5 Hz, H-2), 3.69–3.80 (m, 1 H, H-7), 3.84–3.98 (m, 2 H, H-3,7), 4.19 (quint., 1 H, $J_{5,6}$ 3.5, $J_{6,7}$ 3.5 Hz, H-6), 4.68 (dd, 1 H, $J_{4,5}$ 6.6 Hz, H-4), and 4.02 (dd, 1 H, H-5).

Second component: ^{1}H-n.m.r. (220 MHz): δ 1.38 (s, 3 H, OCC*H*$_3$), 1.46 (d,

3 H, $J_{2,8}$ 7.5 Hz, H_3-8), 1.57 (s, 3 H, OCCH_3), 2.72 (br.s, 1 H, OH), 2.98 (dq, 1 H, $J_{2,3}$ 5.5 Hz, H-2), 3.69–3.80 (m, 1 H, H-7), 3.84–3.98 (m, 2 H, H-3,7), 4.19 (quint., 1 H, $J_{5,6}$ 3.5, $J_{6,7}$ 3.5 Hz, H-6), 4.53 (t, 1 H, $J_{3,4}$ 5.7, $J_{4,5}$ 5.7 Hz, H-4), and 4.82 (dd, 1 H, H-5); m.s.: *m/z* 213 ($M^+ + 1 - CH_3$), 212 ($M^+ - CH_3$), and 196 ($M^+ - OCH_3$).

Equilibration of compounds **19** *and* **24**. — The nitrile **19** (250 mg, 0.92 mmol; ratio of 2-epimers, 1:1) was dissolved in 0.3M sodium ethoxide in dry ethanol (25 mL) and the solution was boiled under reflux for 4 h, after which the reaction was quenched with 1% methanolic HCl. The crude syrup from evaporation was chromatographed (*E*) to give two homogeneous fractions, each of which contained two components (^{1}H-n.m.r.). The less polar component was identical to the starting material **19** and the more polar was the α anomer **24**, in the ratio 1:4.

α Anomer (**24**). R_F 0.34 (*E*), $\nu_{max}^{CHCl_3}$ 3500 (OH) and 2225 cm^{-1} (CN); ^{1}H-n.m.r. (1:1 mixture; 220 MHz): δ 1.34 and 1.38 (s, 3 H, OCCH_3), 1.50 and 1.40 (d, 3 H, $J_{2,8}$ 7.5 Hz, H_3-8), 1.53 and 1.56 (s, 3 H, OCCH_3), 2.04 and 2.30 (br.s, 1 H, OH), 3.02 (m, 1 H, H-2), 3.59–3.77 (m, 2 H, H_2-7), 4.03 and 4.08 (dd, 1 H, $J_{2,3}$ 9.0, $J_{3,4}$ 4.0 Hz, H-3), 4.15 and 4.20 (t, 1 H, $J_{6,7}$ 5.0 Hz, H-6), 4.73–4.80 (m, 1 H, H-5), 4.68 and 4.82 (dd, 1 H, $J_{4,5}$ 6.0 Hz, H-4).

Anal. (h.r.m.s.): Calc. for $C_{10}H_{14}NO_4$ ($M^+ - CH_3$): 212.0922. Found: 212.0921.

Reaction of **13** *with acetonylidenetriphenylphosphorane* (**21**). — Reaction of **13** (250 mg, 1.32 mmol) with **21** (700 mg, 2 mmol) under the standard Wittig reactions conditions was complete within 2 h. Although the product (280 mg, 97%) appeared homogeneous on t.l.c., ^{1}H-n.m.r. showed it to be a mixture of **22** and **23** in 7:3 ratio (integration of the isopropylidene methyl signals).

*4,7-Anhydro-1,3-dideoxy-5,6-*O*-isopropylidene-*D-altro*-oct-2-ulose* (**22**). R_F 0.34 (*H*); $\nu_{max}^{CHCl_3}$ 3420 (OH) and 1715 cm^{-1} (ester C=O); ^{1}H-n.m.r. (220 MHz): δ 1.33 (s, 3 H, OCCH_3), 1.49 (s, 3 H, OCCH_3), 2.20 (s, 3 H, H_3-1), 2.87 (d, 2 H, $J_{3,4}$ 6.0 Hz, H_2-3), 3.59 (d, 2 H, $J_{7,8}$ 5.6 Hz, H_2-8), 4.08 (t, 1 H, H-7), 4.37 (dt, 1 H, $J_{4,5}$ 3.4 Hz, H-4), 4.65 (d, 1 H, $J_{5,6}$ 6.3 Hz, H-6), and 4.75 (dd, 1 H, H-5).

*4,7-Anhydro-1,3-dideoxy-5,6-*D*-isopropylidene-*D-allo*-oct-2-ulose* (**23**). R_F 0.34 (*F*); $\nu_{max}^{CHCl_3}$ 3420 (OH) and 1715 cm^{-1} (ester); ^{1}H-n.m.r. (220 MHz): δ 1.34 (s, 3 H, OCCH_3), 1.54 (s, 3 H, OCCH_3), 2.20 (s, 3 H, H_3-1), 2.68–2.85 (m, 2 H, H_2-3), 3.13 (br.s, 1 H, OH), 3.63 (dd, 1 H, $J_{8a,8b}$ 12.0, $J_{7,8b}$ 3.9 Hz, H-8b), 3.76 (dd, 1 H, $J_{7,8a}$ 3.0 Hz, H-8a), 4.03 (ddd, 1 H, $J_{6,7}$ 4.0 Hz, H-7), 4.25 (ddd, 1 H, $J_{3,4}$ 7.0, $J_{3,4}$ 5.0, $J_{4,5}$ 4.8 Hz, H-4), 4.43 (dd, 1 H, $J_{5,6}$ 6.5 Hz, H-5), and 4.70 (dd, 1 H, H-6), m.s.: *m/z* 215 ($M^+ - CH_3$), 199 ($M^+ - OCH_3$), and 181 ($M^+ - OCH_3 - H_2O$).

Equilibration of compounds **22** *and* **23**. — A portion (230 mg, 0.92 mmol) of the isomeric uloses **22** and **23** was dissolved in methanol (50 mL), a catalytic amount of sodium methoxide added, and the solution stirred at room temperature. The ratio of **22** and **23** was determined periodically by removing an aliquot of the solution, neutralizing with 1% methanolic HCl, evaporation, and determination of the ^{1}H-n.m.r. spectrum. Integration of the isopropylidene methyl signals was used

to determine the ratio of the isomers. After 0.5 h, the ratio of **23** to **22** was 4:1 and remained unchanged thereafter.

Ethyl 5,9-anhydro-2,4-dideoxy-8,10-O-ethylidene-D-glycero-D-ido- (**28**) *and* -D-glycero-D-gulo-*dec-3-ulosonate* (**29**). — To a solution of triphenylphosphine (65 g, 0.28 mol) in benzene (250 mL), was added ethyl 4-bromo-3-oxobutanoate[12] (52 g, 0.33 mol) at such a rate that the temperature did not exceed 30°. After 18 h at room temperature, the precipitate was collected by filtration, washed with benzene, and dried (115 g, 97%). A portion of the salt (40 g, 95 mmol) was stirred vigorously in hot water (1.8 L), Na_2CO_3 (15 g, 0.14 mol) added, and the resulting suspension stirred at room temperature for 12 h. The solid material (**26**) was collected by filtration, washed with water, and dried under vacuum (27 g, 83%). 4,6-*O*-Ethylidene-D-glucopyranose[15] (**25**; 5 g, 14 mmol) was dissolved in acetonitrile (50 mL), the phosphorane **26** (8 g, 20 mmol) added, and the solution boiled under reflux for 72 h, when t.l.c. (*F*) indicated that the reaction was complete. The solvent was removed and the residue partitioned between dichloromethane and water. Evaporation of the organic extract afforded a brown syrup, a portion of which was purified by column chromatography for characterization. Two successive silica gel columns (93:7 dichloromethane–methanol) gave **29** (105 mg) and **28** (100 mg) as oils.

Compound **29**. R_F 0.65 (*F*), $[\alpha]_D^{22}$ +34.6° (*c* 2.23, chloroform); ν_{max}^{film} 3450 (OH), 1735 (ester C=O), and 1715 cm^{-1} (ketone C=O); ^{1}H-n.m.r. (600 MHz): δ 1.1–1.5 (m, 5 H, CH_3CH_2); the rest of the spectrum was too complex for definitive assignments to be made.

Anal. Calc. for $C_{14}H_{22}O_8$: C, 52.83; H, 6.97. Found: C, 53.02; H, 6.82.

Compound **28**. $[\alpha]_D^{24}$ −28.9° (*c* 0.47, chloroform), R_F 0.61 (*F*); ν_{max}^{film} 3480 (OH), 1750 (ester C=O), and 1730 cm^{-1} (ketone C=O); ^{1}H-n.m.r. (600 MHz): δ 1.27 (t, 3 H, J_{CH_3,CH_2} 6.10 Hz, CH_3CH_2), 1.35 (d, 3 H, $J_{CH_3,CH}$ 4.28 Hz, CH_3CH), 2.75 (dd, 1 H, $J_{4,5}$ 7.35, $J_{4a,4b}$ 15.92 Hz, H-4a), 3.01 (dd, 1 H, $J_{4b,5}$ 3.67 Hz, H-4b), 3.23 (dd, 1 H, $J_{7,8}$ and $J_{8,9}$ 9.80 Hz, H-8), 3.32 (ddd, 1 H, $J_{9,10a}$ 9.80, $J_{9,10b}$ 3.68 Hz, H-9), 3.34 (dd, 1 H, $J_{6,7}$ 9.18 Hz, H-7), 3.42 (dd, 1 H, $J_{10a,10b}$ 9.80 Hz, H-10a), 3.48 (d, 1 H, $J_{2a,2b}$ 15.30 Hz, H-2a), 3.52 (d, 1 H, H-2b), 3.68 (dd, 1 H, $J_{5,6}$ 8.57 Hz, H-6), 3.83 (ddd, 1 H, H-5), 4.10 (dd, 1 H, H-10b), 4.19 (q, 2 H, CH_2CH_3), and 4.70 (q, 1 H, $CHCH_3$); the assignments for H-3 and H-4 may be reversed.

Anal. Calc. for $C_{14}H_{22}O_8$: C, 52.83; H, 6.97. Found: C, 52.69; H, 6.96.

Ethyl 5,9-anhydro-2,4-dideoxy-D-glycero-D-ido- (**31**) *and* -D-glycero-D-gulo-*dec-3-ulosonate* **32**. — The crude reaction mixture containing **28** and **29** was dissolved in a mixture of ethanol (250 mL) and 5% (v/v) aqueous H_2SO_4 (24 mL), and the solution boiled under reflux for 4 h, when t.l.c. (*G*) indicated that the reaction was complete. The mixture was made neutral with $NaHCO_3$ and extracted with dichloromethane to remove triphenylphosphine oxide. The aqueous layer was evaporated to dryness and the residue leached repeatedly with ethanol. Evaporation of the ethanol solution gave a yellow oil (3.5 g, 82% from **25**). Column chromatography (*G*) afforded **31** as a clear oil, $[\alpha]_D^{23}$ +5.7° (*c* 0.42, methanol), R_F 0.50 (**G**); ν_{max}^{film} 3400 (OH) and 1720 cm^{-1} (ester and ketone C=O); ^{1}H-n.m.r. (60

MHz, D_2O, external Me_4Si): δ 1.25 (t, 3 H, J_{CH_3,CH_2} 6 Hz, CH_3CH_2), 2.1–3.7 (m, 9 H, H-5,6,7,8,9,10a,10b,4a,4b), and 4.0 (1, 2 H, CH_2CH_3).

Anal. Calc. for $C_{12}H_{20}O_8$: C, 49.31; H, 6.90. Found: C, 49.03; H, 6.80.

Further chromatography afforded **32**, a pale yellow oil, $[\alpha]_D^{23}$ +9.1° (*c* 0.47, methanol), R_F 0.20 (*G*); ν_{max}^{film} 3420 (OH) and 1715 cm^{-1} (ester and ketone C=O); ^{1}H-n.m.r. (60 MHz, D_2O, external Me_4Si): δ 1.25 (t, 3 H, J_{CH_3,CH_2} 6 Hz, CH_3CH_2), 2.1–3.7 (m, 9 H, H-5,6,7,8,9,10a,10b,4a,4b), and 4.0 (q, 2 H, CH_2CH_3).

Anal. Calc. for $C_{12}H_{20}O_8$: C, 49.31; H, 6.90. Found: C, 50.05; H, 7.14.

*Ethyl 5,9-anhydro-2,4-dideoxy-10-*O*-triphenylmethyl-*D-glycero-D-gulo-*and* D-ido-*dec-3-ulosonate* (**33**). — A mixture of the tetrols **31** and **32** (1.331 g, 4.60 mmol) was dissolved in dry pyridine (50 mL) and treated with chlorotriphenylmethane (1.40 g, 5.03 mmol) for two days at room temperature. The mixture was poured into water and extracted with dichloromethane. After washing, drying, concentration, and purification by column chromatography (*F*), a mixture was obtained as a clear oil (1.2 g, 50%), R_F 0.53 and 0.44 (*F*); ν_{max}^{film} 3400 (OH), 1740 (ester C=O), and 1720 cm^{-1} (ketone C=O); ^{1}H-n.m.r. (80 MHz): δ 1.15 (t, 3 H, J_{CH_3,CH_2} 7 Hz, CH_3CH_2), 2.5–3.0 (m, 2 H, H-4a,4b), 3.0–3.8 (m, 9 H, H-5,6,7,8,9,10a,10b,4a,4b), 3.8–4.4 (br.s, 3 H, 3 OH), 4.15 (q, 2 H, CH_2CH_3), and 7.1–7.6 (m, 15 H, arom.).

Anal. Calc. for $C_{31}H_{34}O_8$: C, 69.65; H, 6.41. Found: C, 69.38; H, 6.39.

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SYNTHESIS OF *C*-GLYCOSYL COMPOUNDS BY THE WITTIG IODOCYCLIZATION PROCEDURE. DIFFERENCES FROM MERCURIOCYCLIZATION

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ABSTRACT

Various sugars were *C*-glycosylated by treatment with methylenetriphenylphosphorane and subsequent iodocyclization of the resulting hept- and hex-enitols. In all cases, a *C*-glycofuranosyl compound was obtained, except for 3,4,5,7-tetra-*O*-benzyl-1,2-dideoxy-D-*manno*-hept-1-enitol which yielded a *C*-pyranosyl compound. High stereoselection, with formation of the 1,2-*cis* adduct as major product, was observed when an asymmetric center was present in the position adjacent to the double bond.

INTRODUCTION

C-Glycosyl compounds have recently gained interest as building blocks for the synthesis of a large number of natural products[1] and as potential inhibitors of metabolic processes[2–8]. A two-step procedure to obtain the *C*-glycosyl compounds **3**, first employed by Orhui *et al.*[9], involves the formation of an unsaturated, open-chain derivative **2**, followed by cyclization. For the first step, stabilized Wittig reagents[9–11] or methylenetriphenylphosphorane[4–7,12,13] have been employed. The subsequent cyclization of the unsaturated derivative **2** may occur through a Michael reaction by treatment with bases or, sometimes spontaneously, when stabilized ylids are employed; a mixture of the two anomers is generally formed†. In 1981, Pougny *et al.*[12] introduced activation of the double bond with an electrophile, which represents a more general procedure and, in addition, allows better stereocontrol[7,15–17]. Our recent studies[13] on the stereochemistry of the mercuriocyclization of some polybenzylated enitols have shown that the stereochemical course of the reaction is largely dependent on the configuration at the carbon atom adjacent to the carbonyl group of the starting sugar. We report herein our results on the iodocyclization of some hept- and hex-enitols, which differ to some extent from those obtained in the

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†For some exceptions, see ref. 11 and 14.

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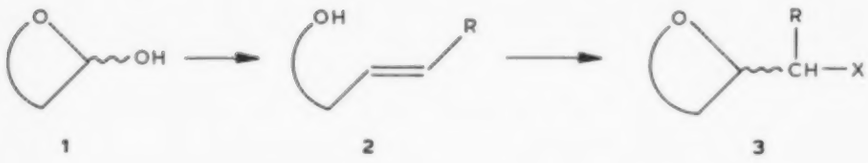


1 2 3

mercury-promoted ring closure.

RESULTS AND DISCUSSION

The Wittig reactions took place at room temperature in oxolane–N,N,N′,N′,N″,N″-hexamethylphosphoric triamide [$(CH_2)_4O$–$(Me_2N)_3PO$] by adding a solution of the sugar (1 equiv.) to the ylid prepared from methyltriphenylphosphonium iodide (5 equiv.) and 1.6M butyllithium in hexane (5 equiv.), under a dry nitrogen atmosphere. The presence of $(Me_2N)_3PO$, in some cases, enchanced the rate of the reaction (**6**, Table I) and allowed better yields (**6**, **9**, and **12**). However, with 2,3,4,6-tetra-*O*-benzyl-D-glucose, the above-mentioned conditions led to an elimination reaction, affording 3,5,7-tri-*O*-benzyl-1,2,4-trideoxy-D-*erythro*-hepta-1,3-dienitol (**5**) in 80% yield. The desired 3,4,5,7-tetra-*O*-benzyl-1,2-deoxy-D-*gluco*-hept-1-enitol (**4**) could be obtained in 54% yield with the procedure previously described[13].

First of all, we performed the iodocyclization on the glucopheptenitol **4**; under Barlett *et al.*[18] cynetic conditions (iodine, sodium hydrogencarbonate, and acetonitrile) or with *N*-iodosuccinimide, the double bond was unreactive*, whereas, under

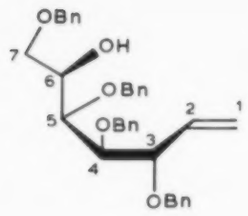
TABLE I

SYNTHESIS OF HEPT- AND HEX-ENITOLS BY WITTIG REACTION WITH METHYLENETRIPHENYLPHOSPHORANE.

Compound formed	*Solvent*	*Ylid (equiv.)*	*Conditions*[a]		*Yield %*
			Temp.[a]	*Time (h)*	
4[b]	$(CH_2)_4O$	2	R.t.,	24	54
5	$(CH_2)_4O$–$(Me_2N)_3PO$	5	R.t.,	18	79
6[b]	$(CH_2)_4O$	2	Reflux,	3	24
6	$(CH_2)_4O$–$(Me_2N)_3PO$	5	R.t.,	2.5	27
7	$(CH_2)_4O$–$(Me_2N)_3PO$	5	R.t.,	1.5	70
9[b]	$(CH_2)_4O$	5	R.t.	3	10
9	$(CH_2)_4O$–$(Me_2N)_3PO$	5	R.t.,	3	41
10 and **11**	$(CH_2)_4O$–$(Me_2N)_3PO$	5	R.t.,	3	45
12[b]	$(CH_2)_4O$	3.5	R.t.,	2.5	21
12	$(CH_2)_4O$–$(Me_2N)_3PO$	5	R.t.,	3	59

[a]R.t., room temperature. [b]Ref. 13.

*This double bond also showed no reactivity towards several epoxidizing reagents, such as 3-chloroperoxybenzoic acid, hydrogen peroxide–acetonitrile, and trifluoroperoxyacetic acid.



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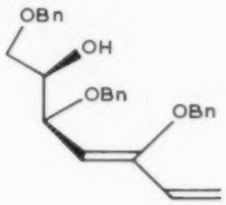

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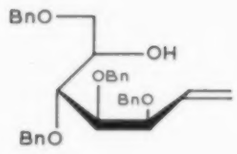

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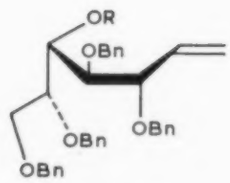
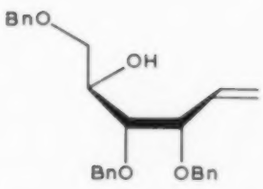


7 R = H
8 R = Bn



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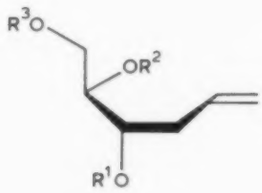


10 $R^1 = R^3 = Bn, R^2 = H$
11 $R^1 = R^2 = Bn, R^3 = H$
12 $R^1 = R^2 = H, R^3 = Tr$

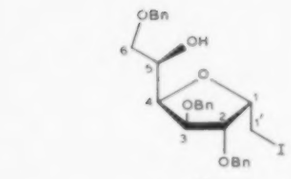
slightly acidic conditions[19] (pH 4, oxolane–water), the compound underwent ring closure to give the *C*-furanosyl derivative **13** (Table II) with concomitant debenzylation at O-5. When other hex- and hept-enitols were subjected to the last-mentioned acidic conditions, in almost all the cases the adduct was a *C*-furanosyl compound, the only exception being the D-*manno*-heptenitol **6** (Table II). When an asymmetric carbon atom was present at the allylic position (**4**, **6**, **7**, **8**, and **9**; Table II), the reaction showed a high stereoselection, always yielding the 1,2-*cis* adduct as the major or sole product. When the allylic position was unsubstituted, (**10**, **11**, and **12**; Table II), almost the same amount of the two anomers was obtained.

TABLE II

REACTION OF HEPT- AND HEX-ENITOLS WITH IODINE[a]

Starting compound	*Resulting compound(s)*	*Ratio*	*Yield (%)*
4	**13**		75
6	**14** and **15**	41:9 (β:α)	42
7	**17**		70
8	**17**		78
9	**18** and **19**	17:3 (α:β)	67
10	**20** and **23**	13:7 (β:α)	72
11	**21** and **24**	21:29 (β:α)	50
12	**22** and **25**	49:51 (β:α)	55

[a]Three equivalents of iodine in oxolane–water at pH 4.



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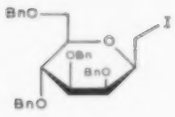

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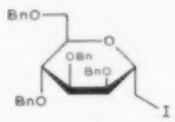

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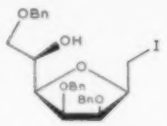

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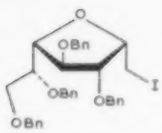

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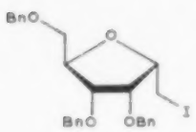

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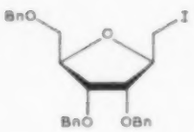

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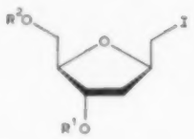
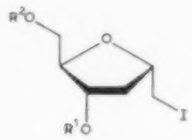
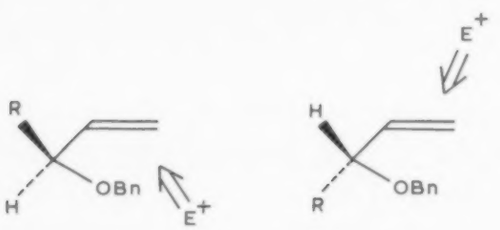


20 $R^1 = R^2 = Bn$
21 $R^1 = Bn, R^2 = H$
22 $R^1 = H, R^2 = Tr$



23 $R^1 = R^2 = Br$
24 $R^1 = Bn, R^2 = H$
25 $R^1 = H, R^2 = Tr$

From a stereochemical point of view, these results are analogous to those obtained when a mercury salt was utilized as promoter of the cyclization; the stereochemistry of the addition of the electrophile showed to be the same, a 1,2-*cis* relationship being obtained in both cases. The stereochemical results may be explained by assuming that the reactive conformations of the enitols are **26** and **27**, in which the allylic oxygen atom lies on about the same plane as that of the double bond, and the electrophile approaches the molecule from the less hindered side.



26 **27**

On the contrary, iodocyclization is quite different from mercuriocyclization with respect to the ring-size of the adducts obtained. Whereas, in the latter case, the free hydroxyl group is the only nucleophile that can promote the internal substitution on the intermediate cation, in the former case, either the hydroxyl or the benzyloxy group can cyclize to yield, in all the cases but one, a furanosyl derivative. The formation of five-membered rings is always preferred over that of six-membered rings; the only exception observed, the formation of a pyranosyl compound from the D-*manno*-heptenitol **6**, may be explained by the overcrowding of a transition state which yields a tetrasubstituted-oxolane ring (**16**) with three 1,2-*cis* interactions[20]. The difference between the factors that determine the ring-size during the closure can be exploited in order to obtain, from the same enitol, either a *C*-glycopyranosyl or a *C*-glycofuranosyl compound only by choosing the proper electrophile; for example, compound **4** gave by treatment with mercury(II) acetate[12] and

iodine, respectively, a six-membered[13] and a five-membered ring. So iodocyclization and mercuriocyclization can become complemental in control of the ring-size.

EXPERIMENTAL

General methods. — Optical rotations were measured with a Perkin–Elmer 241 polarimeter. Analytical t.l.c. was carried out on Merck 60 F_{254} Silica gel plates (0.25-mm layer thickness) and the spots were detected either by a u.v. lamp or by spraying with 50% aqueous H_2SO_4 and heating at 110° for 5 min. Column chromatography was performed with Merck 60 Silica gel (70–230 mesh) and elution with mixtures of hexane–ethyl acetate of various compositions. ^{1}H-N.m.r. spectra were recorded with a Brüker WP-80 or with a Varian XL-200 spectrometer, and ^{13}C-n.m.r. spectra with a Varian XL-100 spectrometer for solutions in $CDCl_3$ containing tetramethylsilane as an internal standard. "Processing" refers to dilution with water, extraction with an organic solvent, washing to neutrality, drying (Na_2SO_4), filtration, and evaporation under reduced pressure.

*(2,3,6-Tri-*O*-benzyl-α-*D*-glucofuranosyl)iodomethane* (**13**). — 3,4,5,7-Tetra-*O*-benzyl-1,2,-dideoxy-D-*gluco*-hept-1-enitol[13] (**4**; 114 mg, 0.21 mmol) was dissolved in oxolane (0.2 mL) and 0.5M (pH 4.0) phtalate buffer (1 mL) was added. A solution of I_2 (161 mg, 0.63 mmol) in oxolane (0.8 mL) was slowly added to the rapidly stirred mixture. After 1 h, the excess of I_2 was eliminated with aqueous Na_2SO_3 and processing afforded a crude product that was chromatographed to yield **13** (91 mg, 75%), oil, $[\alpha]_D^{20}$ −33° (*c* 1.0, chloroform); ^{1}H-n.m.r. (200 MHz): δ 2.6 (bd, 1 H, *J*4 Hz, OH), 3.21 and 3.31 (2 H, AB part of an ABX system, $J_{1'a,1'b}$ 9.5, $J_{1'a,1}$ 5.5, and $J_{1'b,1}$ 10 Hz, CH_2I), 3.4–3.8 (m, 2 H, H-6a, 6b), 4.0–4.2 (m, 4 H, H-2,3,4,5), 4.43 (ddd, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.5–4.6 (m, 6 H, CH_2Ph), and 7.2–7.4 (m, 15 H, Ph); ^{13}C-n.m.r. (100 MHz) δ: 1.2 (CH_2I).

Anal. Calc. for $C_{28}H_{31}IO_5$: C, 58.54; H, 5.44. Found: C, 58.14; H, 5.56.

*3,4,5,7-Tetra-*O*-benzyl-1,2-dideoxy-*D*-manno-hept-1-enitol* (**6**). — A 1.6M hexane solution of butyllitium (8.47 mL, 13.6 mmol) was slowly added to a solution of methyltriphenylphosphonium iodide (5.84 g, 13.6 mmol) in dry oxolane (17 mL) under N_2; dry $(Me_2N)_3PO$ (2.4 mL) was then added, followed by the slow addition of a solution of 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose (1.46 g, 0.271 mmol) in oxolane (5.4 mL) and $(Me_2N)_3PO$ (7.2 mL). After 2.5 h, a saturated aqueous solution of NH_4Cl was added, followed by processing. The crude product was submitted to column chromatography to yield **6** (394 mg, 27%).

Anal. Calc. for $C_{35}H_{38}O_5$: C, 78.04; H, 7.11. Found: C, 77.70; H, 6.99.

*(2,3,4,6-Tetra-*O*-benzyl-β-*D*-mannopyranosyl)iodomethane* (**14**) *and (2,3,4,6-tetra-*O*-benzyl-α-*D*-mannopyranosyl)iodomethane* (**15**). — 3,4,5,7-Tetra-*O*-benzyl-1,2-dideoxy-D-*manno*-hept-1-enitol (**6**) (120 mg, 0.22 mmol) was iodocyclized according to the aforementioned procedure for 3 h. Processing afforded a crude product (110 mg) which was chromatographed on a silica gel column. The main product (63 mg, 42%) was obtained as a mixture of the β- and α- anomer (**14** and **15**)

in a 41:9 ratio. They were separated by careful chromatography on silica gel in 99:1 benzene–ethyl acetate.

Compound **14**. $[\alpha]_D^{20}$ −2° (*c* 1.1, chloroform); ^{1}H-n.m.r. (200 MHz): δ 3.30 (d, 2 H, *J* 7 Hz, CH_2I), 3.49 (ddd, 1 H, $J_{5,6a}$ 2, $J_{5,6b}$ 5.5, and $J_{4,5}$ 9.5 Hz, H-5), 3.55 (dt, 1 H, $J_{1,2}$ 1 Hz, H-1), 3.63 (dd, 1 H, $J_{2,3}$ 2.5, $J_{3,4}$ 9.5 Hz, H-3), 3.67 and 3.77 (2 H, AB part of an ABX system, $J_{6a,6b}$ 11 Hz, H-6a,6b), 3.91 (t, 1 H, *J* 9.5 Hz, H-4), 4.21 (dd, 1 H, H-2), 4.5–5.1 (8 H, m, C*H*$_2$Ph), and 7.1–7.4 (m, 20 H, Ph); ^{13}C-n.m.r. (100 MHz): δ 3.2 (CH_2I).

Anal. Calc. for $C_{35}H_{37}IO_5$: C, 63.26; H, 5.61. Found: C, 63.33; H, 5.50.

Compound **15**. $[\alpha]_D^{20}$ +11° (*c* 0.9, chloroform); ^{1}H-n.m.r. (200 MHz): δ 3.34 and 3.41 (2 H, AB part of an ABX system, $J_{1'a,1'b}$ 10.5, $J_{1'a,1}$ 5.5 $J_{1'b,1}$ 4 Hz), 3.6–4.4 (m, 7 H, H-1,2,3,4,5,6a,6b), 4.4–4.6 (m, 8 H, *CH*$_2$Ph), and 7.1–7.4 (m, 20 H, Ph); ^{13}C- (100 MHz): δ 7.0 (CH_2I).

Anal. Calc. for $C_{35}H_{37}IO_5$: C, 63.26; H, 5.61. Found: C, 63.01; H, 5.42.

3,4,6,7-Tetra-O-*benzyl-1,2-dideoxy*-D-galacto-*hept-1-enitol* (**7**). — 2,3,5,6-Tetra-*O*-benzyl-D-galactofuranose (1.22 g, 0.226 mmol) was subjected to the Wittig reaction according to the aforementioned conditions for 1.5 h. Column chromatography of the crude product yielded **7** (851 mg, 70%), oil, $[\alpha]_D^{20}$ −20° (*c* 1.1, chloroform); ^{1}H-n.m.r. (80 MHz): δ 2.97 (d, 1 H, *J* 6.5 Hz, OH), 3.5–4.0 (m, 5 H, H-4,5,6,7a,7b), 4.20 (ddt, 1 H, $J_{2,3}$ 7, $J_{3,4}$ 3, $J_{3,1a}$, $J_{3,1b}$ 1 Hz, H-3), 4.3–4.9 (m, 8 H, C*H*$_2$Ph), 5.31 and 5.33 (2 H, AB part of an ABMXY system, $J_{1a,1b}$ 2.5, $J_{1a,2}$ 10, $J_{1b,2}$ 18 Hz, H-1a,1b), 6.02 (ddd, 1 H, H-2), and 7.1–7.4 (m, 20 H, Ph).

Anal. Calc. for $C_{35}H_{38}O_5$: C, 78.04; H, 7.11. Found: C, 78.29; H, 7.03.

3,4,5,6,7-Penta-O-*benzyl-1,2-dideoxy*-D-galacto-*hept-1-enitol* (**8**). — NaH (55%, oil dispersion; 49 mg, 1.12 mmol) was washed three times with dry ethyl ether and dissolved into *N,N*-dimethylformamide (1.3 mL) under N_2. Compound **7** (404 mg, 0.75 mmol), dissolved in *N,N*-dimethylformamide (1 mL), was added and the mixture stirred for 1 h at room temperature and 1 h at 50°. The solution was cooled to room temperature and benzyl bromide (0.11 mL, 0.92 mmol) added. After 18 h, a saturated solution of NH_4Cl was added and the crude product obtained after processing was chromatographed on silica gel and eluted with 99:1 benzene–ethyl acetate to yield 3,5,6,7-tetra-*O*-benzyl-1,2,4-trideoxy-D-*threo*-hepta-1,3-dienitol (90 mg, 23%) and **8** (206 mg, 44%), $[\alpha]_D^{20}$ +4° (*c* 1.1, chloroform); ^{1}H-n.m.r. (80 MHz): δ 3.6–4.0 (m, 5 H, H-4,5,6,7a,7b), 4.12 (ddt, 1 H, $J_{2,3}$ 7.5, $J_{3,4}$ 3, $J_{3,1a}$, $J_{3,1b}$ 1 Hz, H-3), 4.3–4.9 (m, 10 H, C*H*$_2$Ph), 5.24 and 5.31 (2 H, AB part of an ABMXY system, $J_{1a,1b}$ 2.5, $J_{1a,2}$ 10, $J_{1b,2}$ 17.5 Hz, H-1a,1b), 5.97 (ddd, 1 H, H-2), and 7.1–7.5 m, 25 H, Ph).

Anal. Calc. for $C_{42}H_{44}O_5$: C, 80.23; H, 7.05. Found: C, 79.85; H, 6.90.

(2,3,5,6-Tetra-O-*benzyl*-α-D-*galactofuranosyl)iodomethane* (**17**). — (*a*) *From* **7**. Compound **7** (112 mg, 0.21 mmol) was iodocyclized according the usual procedure for 40 min to yield, after chromatography, **17** (97 mg, 70%), oil, $[\alpha]_D^{20}$ −39° (*c* 1.0, chloroform); ^{1}H-n.m.r. (200 MHz): δ 3.29 and 3.34 (2 H, AB part of an ABX system, $J_{1'a,1'b}$ 9.5, $J_{1'a,1}$ 6.5, $J_{1'b,1}$ 8 Hz, CH_2I), 3.56 and 3.63 (2 H, AB part of an

ABX system, $J_{6a,6b}$ 10, $J_{6a,5}$ 6, $J_{6b,5}$ 4 Hz, H-6a,6b), 3.77 (ddd, 1 H, $J_{4,5}$ 5.5 Hz, H-5), 4.01 (dd, 1 H, $J_{1,2}$ 4, $J_{2,3}$ 0.5 Hz, H-2), 4.06 (dd, 1 H, $J_{3,4}$ 3.5, H-3), 4.13 (dd, 1 H, H-4), 4.26 (ddd, 1 H, H-1), 4.35–4.8 (m, 8 H, CH_2Ph), and 7.1–7.4 (m, 20 H, Ph); ^{13}C-n.m.r. (100 mHz): δ 0.5 (CH_2I).

Anal. Calc. for $C_{35}H_{37}IO_5$: C, 63.26; H, 5.61. Found: C, 62.85; H, 5.70.

(*b*) *From* **8**. Compound **8** (53 mg, 84 μmol) was iodocyclized according to the usual procedure for 40 min to yield a compound (47 mg, 78%) indistinguishable from **17**, described under (*a*).

*(2,3,5-Tri-*O*-benzyl-α-*D*-ribofuranosyl)iodomethane* (**18**) *and (2,3,5-tri-*O*-benzyl-β-*D*-ribofuranosyl)iodomethane* (**19**). — 3,4,6-Tri-*O*-benzyl-1,2,-dideoxy-D-*ribo*-hex-1-enitol (**9**) (107 mg, 0.256 mmol) was iodocylcized (reaction time; 1 h) to yield, after column chromatography, **18** (79 mg) and **19** (14 mg) (67% overall yield).

Compound **18**. $[\alpha]_D^{20}$ +13° (*c* 1.0, chloroform); ^{1}H-n.m.r. (200 MHz); δ 3.33 and 3.44 (2 H, AB part of an ABX system, $J_{1'a,1'b}$ 9.5, $J_{1'a,1}$ 6.5, $J_{1'b,1}$ 8 Hz, CH_2I), 3.49 and 3.61 (2 H, AB part of an ABX system, $J_{5a,5b}$ 11, $J_{5a,4}$ 4, $J_{5b,4}$ 3 Hz, H-5a,5b), 4.10 (dd, 1 H, $J_{2,3}$ 4, $J_{3,4}$ 7 Hz, H-3), 4.20 (t, 1 H, *J* 4 Hz, H-2), 4.26 (ddd, 1 H, H-4), 4.32 (ddd, 1 H, H-1), 4.4–4.9 (m, 6 H, CH_2Ph), and 7.1–7.4 (m, 15 H, Ph); ^{13}C-n.m.r. (100 MHz): δ 3.6 (CH_2I).

Anal. Calc. for $C_{27}H_{29}IO_4$: C, 59.57; H, 5.37. Found: C, 59.62; H, 4.98.

Compound **19**. $[\alpha]_D^{20}$ −6° (*c* 0.5, chloroform); ^{1}H-n.m.r. (200 MHz): δ 3.24 and 3.29 (2 H, AB part of an ABX system, $J_{1'a,1'b}$ 10.5, $J_{1'a,1}$ 5, $J_{1'b,1}$ 5 Hz, CH_2I), 3.52 (d, 2 H, *J* 4.5 Hz, H-5a,5b), 3.75 (t, 1 H, *J* 5 Hz, H-3 or -2), 3.94 (t, 1 H, *J* 5 Hz, H-2 or -3), 3.95 (q, 1 H, *J* 5 Hz, H-4 or -1), 4.25 (q, 1 H, H-1 or -4), 4.4–4.7 (m, 6 H, CH_2Ph), and 7.1–7.4 (m, 15 Hz, Ph); ^{13}C-n.m.r. (100 MHz): δ 7.8 (CH_2I).

Anal. Calc. for $C_{27}H_{29}IO_4$: C, 59.57; H, 5.37. Found: C, 59.70; H, 5.20.

*4,6-Di-*O*-benzyl-1,2,3-trideoxy-*D*-*erythro*-hex-1-enitol* (**10**) *and 4,5-di-*O*-benzyl-1,2,3-trideoxy-*D*-*erythro*-hex-1-enitol* (**11**). — A 1:2 mixture (700 mg) of 3,5-di-*O*-benzyl-2-deoxy-D-*erythro*-pentose and 3,4-di-*O*-benzyl-2-deoxy-D-*erythro*-pentose were treated with methylenetriphenylphosphorane under the conditions just described for 3 h to yield after chromatography, **10** (104 mg) and **11** (209 mg) (45% overall yield).

Compound **10**. $[\alpha]_D^{20}$ +25° (*c* 1.0, chloroform); ^{1}H-n.m.r. (80 MHz): δ 2.36 (d, 1 H, *J* 4.5 Hz, OH), 2.42 (bt, 2 H, *J* 7 Hz, H-3), 3.4–3.7 (m, 3 H, H-4,6a,6b), 4.88 (m, 1 H, H-5), 4.4–4.8 (m, 4 H, CH_2Ph), 5.0–5.3 (m, 2 H, H-1a,1b), 5.92 (ddt, 1 H, $J_{2,3}$ 7, $J_{1a,2}$ 10, $J_{1b,2}$ 17 Hz, H-2), and 7.1–7.4 (m, 10 H, Ph).

Anal. Calc. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 77.03; H, 7.61.

Compound **11**. $[\alpha]_D^{20}$ +7° (*c* 0.8, chloroform); ^{1}H-n.m.r. (80 MHz): δ 2.18 (bt, 1 H, *J* 6 Hz, OH), 2.44 (bt, 2 H, *J* 6.5 Hz, H-3), 3.4–3.9 (m, 4 H, H-4,5,6a,6b), 4.4–4.8 (m, 4 H, CH_2Ph), 5.0–5.3 (m, 2 H, H-1a,1b), 5.87 (ddt, 1 H, $J_{2,3}$,7 $J_{1a,2}$ 9.5, $J_{1b,2}$ 17 Hz, H-2), and 7.1–7.4 (m, 10 H, Ph).

Anal. Calc. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.90; H, 7.40.

*(3,5-Di-*O*-benzyl-2-deoxy-β-*D*-*erythro*-pentofuranosyl)iodomethane* (**20**) *and (3,5-di-*O*-benzyl-2-deoxy-α-*D*-*erythro*-pentofuranosyl)iodomethane* (**23**). — Com-

pound **10** (80 mg, 0.255 mmol) was iodocyclized for 2 h to yield, after column chromatography on silica gel and elution with 99:1 benzene–ethyl acetate, **20** (52 mg) and **23** (28 mg) (72% overall yield).

Compound **20** *(higher* R_F*).* $[\alpha]_D^{20}$ +11° (*c* 1.0, chloroform); ^{1}H- (200 MHz): δ 2.06 (ddd, 1 H, $J_{2a,1}$ 4.5, $J_{2a,2b}$ 13.5, $J_{2a,3}$ 4 Hz, H-2a), 2.33 (ddd, 1 H, $J_{2b,1}$ 7, $J_{2b,3}$ 6.5 Hz, H-2b), 3.33 and 3.35 (2 H, AB part of an ABX system, $J_{1'a,1'b}$ 10, $J_{1,1'a}$ 8, $J_{1,1'b}$ 6.5 Hz, H-1'a,1'b), 3.46 and 3.49 (2 H, AB part of an ABX system, $J_{5a,5b}$ 10 Hz, $J_{5a,4}$ 5, $J_{5b,4}$ 4.5 Hz, H-5a,5b), 4.05–4.15 (m, 2 H, H-3,4), 4.33 (dddd, 1 H, H-1), 4.4–4.7 (m, 4 H, C*H*$_2$Ph), and 7.30 (s, 10 H, Ph).

Anal. Calc. for $C_{20}H_{23}IO_3$: C, 54.81; H, 5.29. Found: C, 54.54; H, 5.06.

Compound **23** *(lower* R_F*).* $[\alpha]_D^{20}$ +27° (*c* 1.1, chloroform); ^{1}H-n.m.r. (200 MHz): δ 1.76 (ddd, 1 H, $J_{2a,1}$ 9.5, $J_{2a,2b}$ 13.5, $J_{2a,3}$ 6.5 Hz, H-2a), 2.21 (ddd, 1 H, $J_{2b,1}$ 5.5, $J_{2b,3}$ 2 Hz, H-2b), 3.24 and 3.30 (2 H, AB part of an ABX system, $J_{1'a,1'b}$ 10, $J_{1,1'a}$ 6.5, $J_{1,1'b}$ 5 Hz, H-1'a,1'b), 3.46 and 3.54 (2 H, AB part of an ABX system, $J_{5a,5b}$ 10 Hz, $J_{5a,4}$ 5.5, $J_{5b,4}$ 5 Hz, H-5a,5b), 4.05–4.3 (m, 3 H, H-13,4), 4.50 and 4.55 (2s, 4 H, CH_2Ph), and 7.30 (s, 10 H, Ph).

Anal. Calc. for $C_{20}H_{23}IO_3$: C, 54.81; H, 5.29. Found: C, 54.66; H, 5.15.

*(3-*O*-Benzyl-2-deoxy-*α*-*D*-*erythro*-pentofuranosyl)iodomethane* (**24**) *and (3-*O*-Benzyl-2-deoxy-*β*-*D*-*erythro*-pentofuranosyl)iodomethane* (**21**). — Compound **11** (130 mg, 0.414 mmol) was iodocyclized for 2 h to yield, after column chromatography, **24** (42 mg) and **21** (30 mg) (50% overall yield).

Compound **24** *(higher* R_F*).* $[\alpha]_D^{20}$ +18° (*c* 0.5, chloroform); ^{1}H-n.m.r. (200 MHz): δ 1.79 (ddd, 1 H, $J_{2a,1}$ 9.5, $J_{2a,2b}$ 13.5, and $J_{2a,3}$ 6.5 Hz, H-2a), 1.9 (m, 1 H, OH), 2.14 (ddd, 1 H, $J_{2b,1}$ 5.5, $J_{2b,3}$ 2 Hz, H-2b), 3.32 and 3.43 (2 H, AB part of an ABX system, $J_{1'a,1'b}$ 10.5, $J_{1,1'a}$ 4, $J_{1,1'b}$ 5 Hz, H-1'a,1'b), 3.58 and 3.78 (m, 2 H, after D_2O addition, the signal becomes the AB part of an ABX system, $J_{5a,5b}$ 9.5 Hz, $J_{5a,4}$ 3.5, $J_{5b,4}$ 4.5 Hz, H-5a,5b), 3.96 (dddd, 1 H, H-1), 4.05–4.2 (m, 2 H, H-3,4), 4.49 and 4.53 (2 H, ABq, *J* 11.5 Hz, C*H*$_2$Ph), and 7.32 (s, 5 H, Ph).

Anal. Calc. for $C_{13}H_{17}IO_3$: C, 44.85; H, 4.92. Found: C, 44.95; H, 4.83.

Compound **21** *(lower* R_F*).* $[\alpha]_D^{20}$ +9° (*c* 0.5, chloroform); ^{1}H-n.m.r. (200 MHz): δ 1.9 (m, 1 H, OH), 2.06 (ddd, 1 H, $J_{2a,1}$ 4.5, $J_{2a,2b}$ 13.5, $J_{2a,3}$ 4.5 Hz, H-2a), 2.32 (ddd, 1 H, $J_{2b,1}$ 6.5, $J_{2b,3}$ 6.5 Hz, H-2b), 3.3–3.8 (m, 4 H, H-1'a,1'b,5a,5b), 4.0–4.4 (m, 3 H, H-1, 3,4), 4.52 (s, 2 H, C*H*$_2$Ph), and 7.30 (s, 5 H, Ph).

Anal. Calc. for $C_{13}H_{17}IO_3$: C, 44.85; H, 4.92. Found: C, 45.28; H, 4.79.

*1,2,3-Trideoxy-6-*O*-triphenylmethyl-*D*-erythro-hex-1-enitol* (**12**). — 2-Deoxy-5-*O*-triphenylmethyl-*D*-*erythro*-pentose (438 mg) was treated with methylenetriphenylphosphorane under the aforementioned conditions for 4 h to yield **12** (256 mg, 59%).

Anal. Calc. for $C_{25}H_{26}O_3$: C, 80.18; H, 7.00. Found: C, 79.81; H, 6.89.

*(2-Deoxy-5-*O*-triphenylmethyl-*β*-*D*-erythro-pentofuranosyl)iodomethane* (**22**) *and (2-deoxy-5-*O*-triphenylmethyl-*α*-*D*-erythro-pentofuranosyl)iodomethane* (**25**). — Compound **12** (165 mg) was iodocyclized for 2 h to yield, after chromatography, **22** (60 mg) and **25** (62 mg) (55% overall yield).

Compound **22** *(higher* R_F*).* $[\alpha]_D^{20}$ $-3°$ (*c* 1.0, chloroform); ^{1}H-n.m.r. (200 MHz): δ 1.85 (ddd, 1 H, $J_{2a,1}$ 6, $J_{2a,2b}$ 13.5, $J_{2a,3}$ 5 Hz, H-2a), 2.34 (ddd, 1 H, $J_{2b,1}$ 6.5, $J_{2b,3}$ 7 Hz, H-2b), 2.0 (m, 1 H, OH), 3.12 and 3.25 (2 H, AB part of an ABX system, $J_{5'a,5'b}$ 10, $J_{5'a,4}$ 6, $J_{5'b,4}$ 4 Hz, H-5a,5b), 3.34 and 3.38 (2 H, AB part of an ABX system, $J_{1'a,1'b}$ 10, $J_{1,1'a}$ 6, $J_{1,1'b}$ 6.5 Hz, H-1'a,1'b), 4.09 (ddd, 1 H, $J_{3,4}$ 4 Hz, H-4), 4.26 (dddd, 1 H, H-1), 4.36 (m, 1 H, after D_2O exchange the signal becomes a ddd, H-3), and 7.2–7.5 (m, 15 H, Ph).

Anal. Calc. for $C_{25}H_{25}IO_3$: C, 60.01; H, 5.04. Found: C, 59.75; H, 4.92.

Compound **25** *(lower* R_F*).* $[\alpha]_D^{20}$ $+12°$ (*c* 1.0, chloroform); ^{1}H-n.m.r. (200 MHz): δ 1.86 (ddd, 1 H, $J_{2a,1}$ 9.5, $J_{2a,2b}$ 13.5, $J_{2a,3}$ 6.5 Hz, H-2a), 2.07 (ddd, 1 H, $J_{2b,1}$ 6.5, $J_{2b,3}$ 3 Hz, H-2b), 3.14 and 3.28 (2 H, AB part of an ABX system, $J_{1'a,1'b}$ 10, $J_{1,1'a}$ 6, $J_{1,1'b}$ 5 Hz, H-1'a,1'b), 3.23 and 3.29 (2 H, AB part of an ABX system, $J_{5a,5b}$ 10, $J_{5a,4}$ 7, $J_{5b,4}$ 5 H, H-5a,5b), 4.00 (ddd, 1 H, $J_{3,4}$ 3 Hz, H-4), 4.22 (dddd, 1 H, H-1), 4.35 (m, 1 H, after D_2O exchange the signal becomes a ddd, H-3), and 7.2–7.5 (m, 15 H, Ph).

Anal. Calc. for $C_{25}H_{25}IO_3$: C, 60.01; H, 5.04. Found: C, 59.63; H, 4.84.

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C-GLUCOSYLARENES FROM *O*-α-D-GLUCOSYL TRICHLOROACETIMIDATES. STRUCTURE OF BERGENIN DERIVATIVES*

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ABSTRACT

C-Glucosylation of oxysubstituted benzene derivatives with *O*-α-D-glucopyranosyl trichloroacetimidate gave mainly β-D-glucopyranosylarenes. The most efficient catalysts were diethyl ether·boron trifluoride, diethyl ether·zinc chloride, and zinc chloride. The reaction was successful with fully and partially *O*-protected phloroglucinols and it was also compatible with an additional *C*-alkyl substituent. Introduction of an electron-withdrawing, *C*-acetyl substituent into the phloroglucinol structure lowered the reactivity. The reaction could be extended to 1,2,3- and 1,2,4-trioxysubstituted benzene derivatives to give the bergenin derivative (3*R*,4*R*,4a*R*,10b*S*)-3,4-diacetoxy-2-acetoxymethyltetrahydropyrano[5,6-*C*]-3,4-dihydroisocoumarin *via* an intramolecular version of this reaction. O-Protected resorcinols and *C*-substituted derivatives of dioxysubstituted benzenes gave various 4-*C*-glucosyl-benzene and chroman derivatives. An anomeric mixture of *C*-glucosyl derivative of anthrone was obtained from 9-trimethylsilyloxyanthracene (as a monoxysubstituted benzene derivative). The pure β-D anomer was synthesized from the *O*-acylated trichloroacetimidate.

INTRODUCTION

C-Glycosylarenes, and amongst these especially *C*-glucosylarenes, are widespread in Nature and they have been isolated from very different sources[1]. They are of interest as natural dye-stuffs (vitexin[2], carminic acid[2]) and as compounds having interesting physiological properties (*C*-glycosyltetrahydrocannabinol[3], hedamycin[4], kyanamycin[4], bergenin[5–7], etc.). Improved antitumor activity is expected from *C*-glycosylanthracyclinones due to differences in their metabolism[8]. Most of the compounds mentioned are derivatives of oxysubstituted benzenes and benzoquinones, for which an interesting hypothesis for antitumor activity has been proposed[9].

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O-Glycopyranosyl trichloroacetimidates have proven to be excellent glycosyl donors with silylenol ethers as *C*-acceptors[10]. Therefore, oxy-substituted benzene derivatives would be substrates in this Friedel–Crafts type reaction as well[11]. Earlier Friedel–Crafts type reactions with glycopyranosyl halides gave frequently both anomers and unsatisfactory results because of low reactivity[12]. Considerably lower reactivity has been observed for pyranoses as compared to furanoses[13].

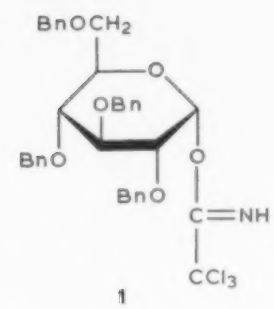
RESULTS AND DISCUSSION

Our preliminary investigations[11] with *O*-α-D-glucopyranosyl trichloroacetimidate (**1**), phloroglucinol trimethyl ether, and diethyl ether·boron trifluoride as catalyst gave excellent yields of the β-D-glucosyl compound **2**, making the yield of this method competitive with those of any other reported methods[12–14]. In the meantime also, the *O*-β-D-glucopyranosyl imidate **11** could be successfully used[15] for the synthesis of compound **2**. Therefore, we undertook a more detailed investigation[15] of the scope of this *C*-glucosyl-bond-forming reaction with the glucosyl donor **1**.

Electron-rich benzene derivatives are labile to acid treatment; therefore, the selection of the catalyst system was crucial for these reactions. A thorough investigation of various Lewis-acid catalysts revealed that, besides the efficient diethyl ether·borontrifluoride catalyst*, the weak Lewis-acids, diethyl ether·zinc chloride and zinc chloride itself, are the most efficient catalysts. This result was clearly demonstrated with phloroglucinol tribenzyl ether and imidate **1**, which yielded, with diethyl ether·zinc chloride as catalyst, clearly the corresponding β-*C*-glucosyl compound **3** as main product, in addition to some α-D anomer (89%; ratio of β to α, 3:1). Diethyl ether·borontrifluoride led mainly to the decomposition of the glucosyl acceptor[14].

Investigations of various substituted phloroglucinol derivatives gave interesting results. With the dimethyltrimethylsilyl ether of phloroglucinol and diethyl ether·borontrifluoride, only the regioisomer **4** could be isolated. However, the dimethyl-*O*-(1,1-dimethylethyl)diphenylsilyl ether afforded, under the same conditions, preponderantly the regioisomer **5** (62%; ratio of **5** to **4** 3:1). For structural assignments, **4** was debenzylated and subsequently *O*-acetylated to give **6**. Compounds **2–5** are suitable starting materials for *C*-glucosylflavone syntheses. This is even more so for the *C*-glucosyl compound **7**, which was obtained from methyl 2,4,6-trimethoxyphenylpropionate in high yield. It was transformed into the *O*-acetyl derivative **8**. 2-Isopropenylphloroglucinol trimethyl ether gave with diethyl ether·zinc chloride as catalyst, the regioisomers **9** and **12** owing to electrophilic attack at the benzene nucleus or at the electron-rich side chain, followed by prototropy. Introduction of an electron withdrawing substituent into the phloroglucinol residue led to lowered reactivity; for instance, 2-acetylphloroglucinol dimethyl

*This catalyst system[16] was mainly used for *O*-glycosyl trichloroacetimidate activation.



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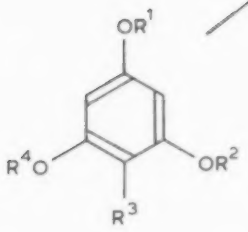

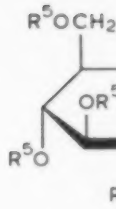

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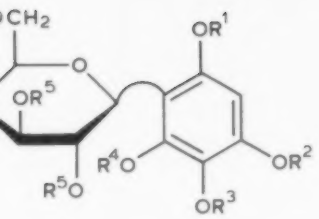

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$= Me, R^3 = H, R^4 = R^5 = Ac$
$= R^4 = Me, R^3 = (CH_2)_2CO_2Me, R^5 = Bn$
$= R^4 = Me, R^3 = (CH_2)_2CO_2Me, R^5 = Ac$
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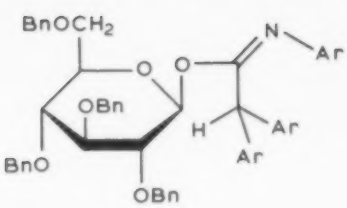

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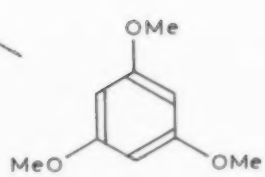

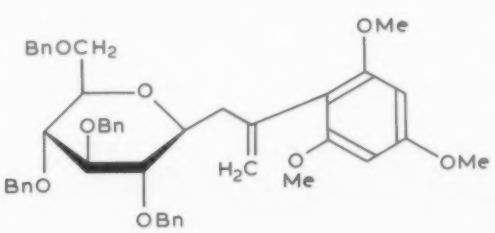

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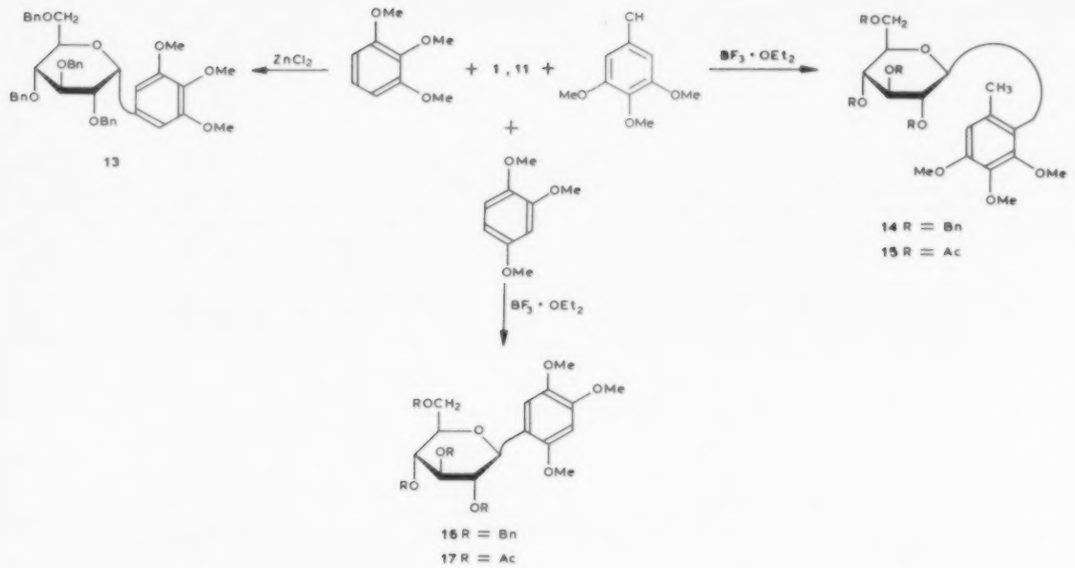
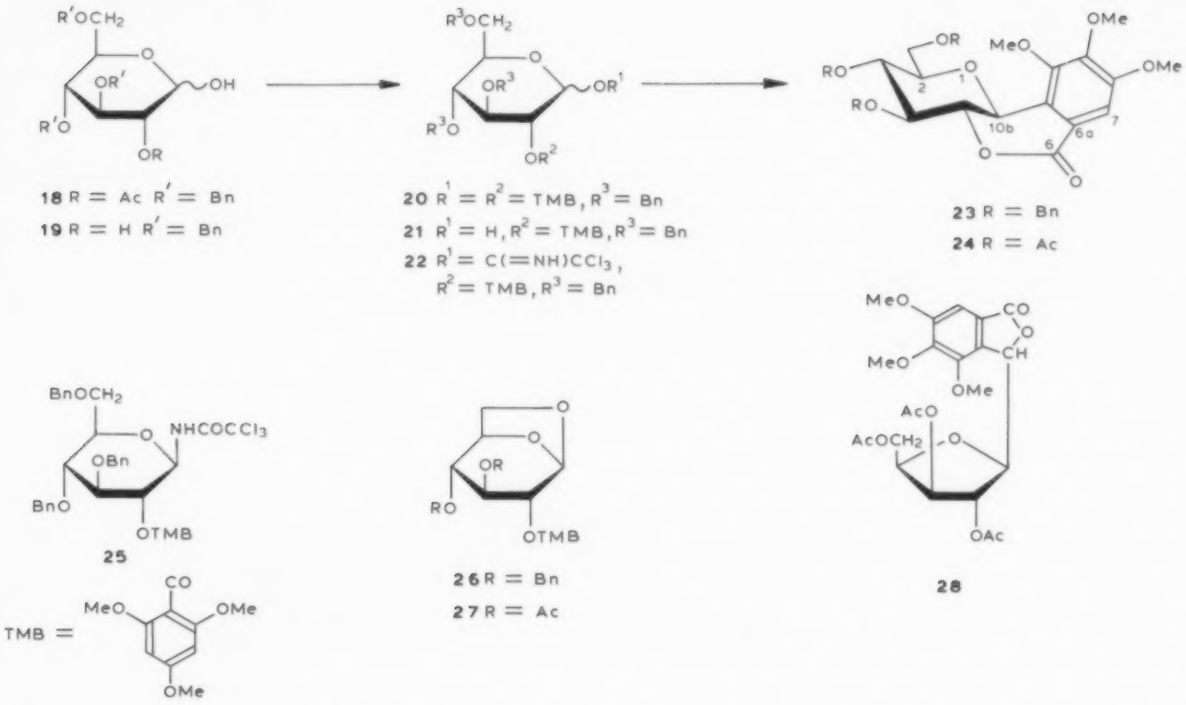


ether afforded the *C*-glucosyl compound **10** only in a modest yield.

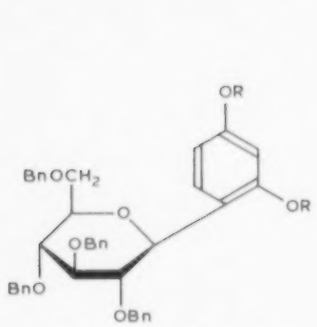
The result obtained for compound **10** lowered our expectations for the regioisomeric trimethoxy-substituted benzene derivatives, since one of the methoxy groups would inductively deactivate the benzene nucleus for electrophilic attack. This was also observed with pyrogallol trimethyl ether; only the α-D isomer **13** was obtained in low yield. However, treatment of the 5-methyl-substituted derivative with imidate **11** exhibited a very different behavior; the β-D isomer **14** was isolated again in fairly good yield (47%); only traces (3%) of the corresponding α-D isomer could be isolated. Also, 1,2,4-trimethoxybenzene gave the *C*-β-D-glucosyl compound **16** from **1** in reasonable yield. For structural assignments, compounds **14** and **16** were transformed into the *O*-acetyl derivatives **15** and **17**, respectively.

The results obtained for compound **14** were quite promising for a short synthesis of the *O*-acylated bergenin dimethyl ether[6,7] **24** *via* an intramolecular *C*-glucosyl-bond formation. Bergenin-type compounds have been isolated from a heartwood extraction of *Macaranga peltata*, a small tree commonly found in Indian forests. A gum powder of this tree has been used in Indian medicine for the treatment of veneral diseases[7]. In our approach, the D-glucose derivative **18** was synthesized from the easily available 3,4,6-tri-*O*-acetyl-1,2-*O*-(1-methoxyethylidene)-D-glucose[17], and deacetylation gave **19**. Treatment with 3,4,5-trimethoxybenzoyl chloride in the presence of methylpyridine in toluene afforded the 1,2-digalloyl-D-glucose derivative **20**, which was selectively transformed into the 2-galloyl derivative **21** by treatment with hydrazine acetate. The α and β mixture of trichloroacetimidates **22** was obtained with trichloroacetonitrile–potassium carbonate and subsequent addition of sodium hydride in almost quantitative yield (98%; ratio of α to β, 6:1); potassium carbonate alone gave a 2:1 ratio of the anomers.

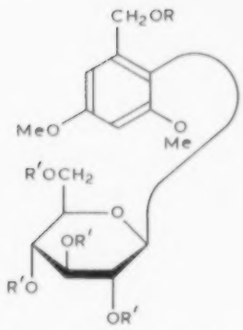


Several methods were investigated for the intramolecular ring-closure of the trichloroacetimidates **22**. For instance, treatment of the α-D anomer of **22** with trifluoromethanesulfonic acid as catalyst gave, *via* imidate rearrangement, the glucosylamine derivative **25** in good yield. Other strong Lewis acids led to the formation of some additional 1,6-anhydro-D-glucose derivative **26**, which was also obtained from the β-D anomer of **22** with diethyl ether·zinc chloride as catalyst; the main product in the latter reaction was compound **21**. Borontrifluoride treatment of the α-D anomer of trichloroacetimidate **22** in toluene afforded, in addition to some 1,6-anhydro-D-glucose derivative **26**, a new compound **23**, which after hydrogenolytic debenzylation and *O*-acetylation had ^{1}H-n.m.r. spectral data in agreement with structure **24** proposed for bergenin dimethyl ether[6,7]. All the sugar ring protons could be fully assigned by the use of different solvents. Their chemical shifts and coupling constants are in accordance with expectations, $J_{1',2'}$ 7.8, $J_{2',3'}$ 9.5, $J_{3',4'}$ 9.5, $J_{4',5'}$ 9.5, $J_{5',6'}$ 5.2, and $J_{5',6''}$ 2.5 Hz; however, these data are not in agreement with the published data for the natural product[7]. In our opinion, the ^{1}H-n.m.r. and mass spectral data published for the natural product rather suggest structure **28**; however, further work is required for the final structural elucidation of this compound.

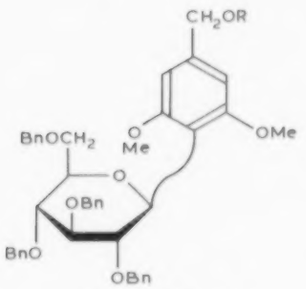
Various 1,3-dioxybenzenes could be successfully *C*-glucosylated with the trichloroacetimidate **1**. Resorcinol dimethyl ether and resorcinol bis(trimethylsilyl) ether gave the *C*-glucosyl components **29** and **30**, respectively, in high yield. [(1,1-Dimethyl)ethyl](diphenyl)silyloxymethyl resorcinal dimethyl ether afforded a 2:1 mixture of the regioisomers **31** and **34**, which were immediately desilylated with tetrabutylammonium fluoride and isolated as compounds **32** and **35** in good yield.



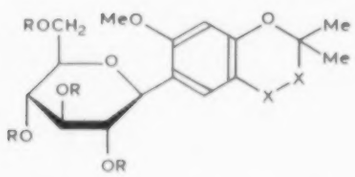
29 R = Bn, R' = Me
30 R = Bn, R' = H



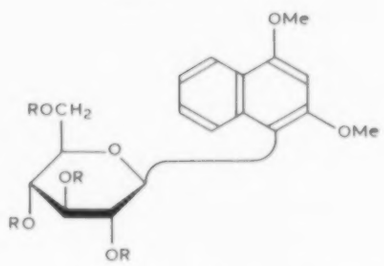
31 R = Bu^tPh_2Si, R' = Bn
32 R = H, R' = Bn
33 R = R' = Ac



34 R = Bu^tMe_2Si
35 R = H

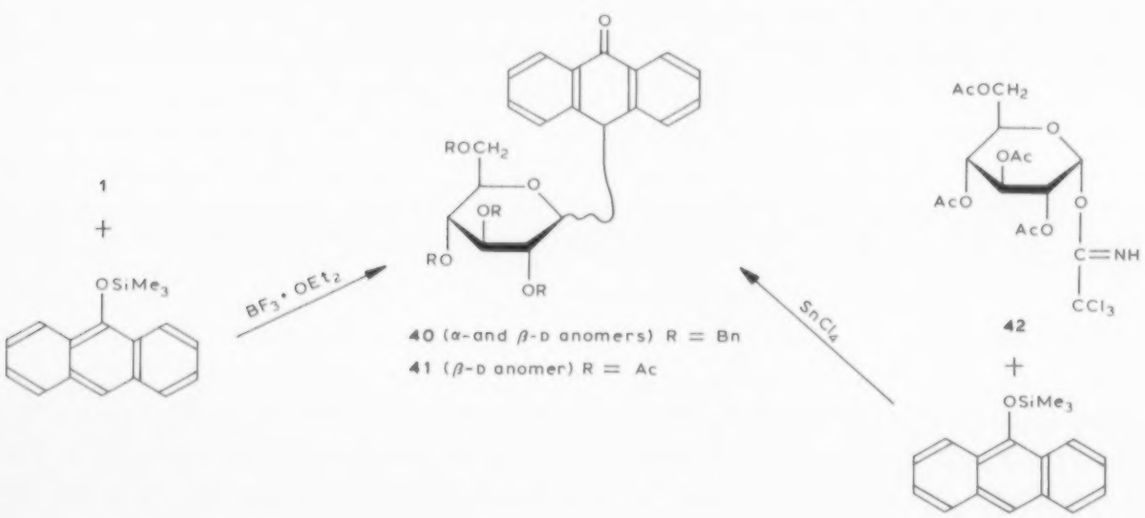


36 R = Bn, X-X = CH=CH
37 R = Ac, X-X = CH_2—CH_2



38 (Rotamers) (a and b), R = Bn
39 R = Ac

Compound **32** was also transformed into the *O*-acetyl derivative **33**. The occurrence of the oxysubstituted chromene and naphthalene nuclei in natural *C*-glucosyl compounds led us to investigate the *C*-glucosylation of 7-methoxy-2,2-dimethyl-2*H*-chromene and 1,3-dimethoxynaphthalene as 1,3-dialkoxybenzene derivatives. Thus, the *C*-glucosyl compounds **36** and **38** were obtained and, after hydrogenolytic debenzylation and *O*-acetylation, the *C*-glucosyl compounds **37** and **39**. Restricted rotation around the *C*-glucosyl bond was observed in ^{1}H-n.m.r. measurements, for instance for compounds **6, 7, 8, 33,** and **39**. A clear separation of the two 1,2-rotamers was possible with the *C*-glucosylnaphthalene **38**.



40 (α- and β-D anomers) R = Bn
41 (β-D anomer) R = Ac
42

Simple monoalkoxy-benzenes were not reactive enough for this *C*-glucosyl-bond-forming reaction. However, 9-trimethylsilyloxyanthracene gave a mixture of the anomers of the *C*-glucosylanthrone **40** which could not be separated. The pure *C*-β-D-glucosyl compound **41** was obtained with the *O*-acetylated *O*-α-D-glucopyranosyl trichloroacetimidate **42**.

The structures of the new compounds (anomeric configuration and regioisomeric constitution) were assigned by ^{1}H- and ^{13}C-n.m.r. data. Off-resonance spectra and spectra recorded at high temperature were obtained, some compounds being converted into *O*-acetyl derivatives (**6, 8, 15, 17, 24, 33, 37,** and **39**). The *O*-benzyl compounds **32** and **38** (rotamers) seem to have a twisted conformation according to the coupling constants; this may be due to steric strain around the glycosidic bond. For compound **41**, the ^{1}H-n.m.r. spectral assignments reported[18] could not be verified. The observed preferential formation of *C*-β-D-glucopyranosyl compounds from trichloroacetimidate **1**, contrary to the findings with silylenol ethers as acceptors[10], could be due to a lower steric strain in the β-transition state for the sterically-demanding acceptors used in the present study. This view is supported by the exclusive isolation of the *C*-α-D-glucopyranosyl derivative **13** with the less-hindered pyrogallol trimethyl ether.

EXPERIMENTAL

General. — Melting points are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 MC polarimeter. ^{1}H-N.m.r. and ^{13}C-n.m.r. spectra were recorded, for solution in the solvents noted (Me_4Si, 0.00 δ), with Bruker WP 80 CW, Bruker WM 250 Cryospec, and Jeol FX 90 Q instruments. R_F values refer to t.l.c. performed on silica gel (Merck) with the solvent systems noted. Column chromatography was performed under normal pressure with silica gel (Merck, 70–230 mesh ASTM and 230–400 mesh ASTM for flash chromatography) and under elevated pressure with silica gel (Merck, "LiChroprep" Si 60, 40–60 μm) with the solvent systems noted (petroleum ether, 40–70°).

The following starting materials were commercially available and purchased from Aldrich Co.: 1,3,5-Trimethoxybenzene, 3,4,5-trimethoxytoluene, 1,2,4-trimethoxybenzene, 1,3-dimethoxybenzene, precocene I (2,2-dimethyl-7-methoxy-2*H*-chromene), and 1,3-dimethoxynaphthalene.

*2,4,6-Trimethoxy-1-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)benzene*[11] (**2**). — (*a*) *From* O-*(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl) trichloroacetimidate*[19] (**1**). A solution of **1** (2.06 g, 3 mmol) and 1,3,5-trimethoxybenzene (0.50 g, 3 mmol) in dichloromethane (20 mL) was treated with 0.5M diethyl ether·BF_3 solution in anhydrous dichloromethane (6 mL, 3 mmol) at room temperature. After 3 h, excess saturated solution of $NaHCO_3$ in water was added. The organic layer was separated, dried (Na_2SO_4), and evaporated. The oily residue was purified on silica gel by flash chromatography (4:1, v/v, petroleum ether–ethyl acetate); yield 1.55 g (76%), colorless oil, $[\alpha]_{578}^{20}$ +5.4° (*c* 1.0, chloroform); R_F (4:1, v/v, petroleum

ether–ethyl acetate) 0.35. The physical data have been confirmed independently[13].

Anal. Calc. for $C_{43}H_{46}O_8$ (690.8): C, 74.75; H, 6.71. Found: C, 74.36; H, 6.72.

(*b*) *From* O-*(2,3,4,6-tetra-*O*-benzyl-β-*D*-glucopyranosyl)* N,*2,2-tri-(4-chlorophenyl)acetimidate*[20] (**11**). A solution of **11** (1.05 g, 1.15 mmol) and 1,3,5-trimethoxybenzene (0.33 g, 1.96 mmol) in anhydrous dichloromethane (10 mL) was treated with 0.1M diethyl ether · BF_3 solution in dichloromethane (2 mL, 0.2 mmol) at room temperature. After 20 min, the reaction mixture was worked-up, as described above, to yield **2** (0.53 g, 67%) having identical physical data.

*2,4,6-Tribenzyloxy-1-(2,3,4,6-tetra-*O*-benzyl-β-* (**3**) *and -α-*D*-glucopyranosyl)benzene.* — (*a*) *Synthesis of 1,3,5-tribenzyloxybenzene.* To a solution of 1,3,5-trihydroxybenzene (3.96 g, 24.4 mmol) in anhydrous *N,N*-dimethylformamide (50 mL) was added NaH (2.50 g, 104.2 mmol) under N_2 at −20° and, after 1 h, benzyl bromide (14.08 g, 82.3 mmol). The mixture was kept for 2 h at −20°, then methanol was added to eliminate the excess of NaH, and the suspension was treated with water (100 mL). The organic material was extracted with dichloromethane (3 × 70 mL) and the organic phase dried ($MgSO_4$) and evaporated. The solid residue crystallized from ethanol–water to yield 7.32 g (76%), m.p. 89°; lit.[21] m.p. 39–41° (acetic acid); ^{1}H-n.m.r. (80 MHz, $CDCl_3$): δ 7.48–7.15 (m, 15 H, 3 C_6H_5), 6.63 (s, 3 H, H-2,4,6), and 5.01 (s, 6 H, 3 CH_2).

Anal. Calc. for $C_{27}H_{24}O_3$ (396.5): C, 81.79; H, 6.10. Found: C, 81.86; H, 6.11.

(*b*) *Synthesis of a mixture of* **3** *and its α-*D *anomer.* As described for the preparation of **2**, procedure (*a*) was applied to a solution, in anhydrous dichloromethane (15 mL) of **1** (0.95 g, 1.38 mmol), 1,3,5-tribenzyloxybenzene (0.55 g, 1.38 mmol), and 0.56M diethyl ether · zinc chloride in anhydrous dichloromethane (10 mL, 5.60 mmol) to give, after 1 h, an oily residue that was purified on silica gel by flash chromatography (4:1, v/v, petroleum ether–ethyl acetate), yield 1.13 g (88%; ratio of β- to α-D anomer, 3:1), colorless oil; R_F (4:1, v/v, petroleum ether–ethyl acetate) 0.54; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 7.51–6.91 (m, 35 H, 7 C_6H_5), 6.25, 6.24 (2 s, 2 H, H-4,6), 5.99 (dd, 0.25, H, $J_{1',2'}$ 6.1 Hz, H-1′,α), and 5.19–3.44 (m, 20.75 H).

Anal. Calc. for $C_{61}H_{58}O_8$ (919.1): C, 79.71; H, 6.36. Found: C, 79.63; H, 6.48.

*3,5-Dimethoxy-2-(2,3,4,6-tetra-*O*-benzyl-β-*D*-glucopyranosyl)phenol* (**24**) *and 3,5-dimethoxy-4-(2,3,4,6-tetra-*O*-benzyl-β-*D*-glucopyranosyl)phenol* (**5**). — (*a*) *Synthesis of 3,5-dimethoxy-1-trimethylsilyloxybenzene.* 3,5-Dimethoxyphenol (1.00 g, 6.49 mmol) was refluxed in hexamethyldisilazane (5 mL) and chlorotrimethylsilane (5 mL) for 12 h. Distillation gave a colorless liquid (1.38 g, 94%), b.p. 72° (25 Pa); ^{1}H-n.m.r. (80 MHz, $CDCl_3$): δ 6.28–6.15 (m, 3 H, C_6H_3), 3.80 (s, 6 H, 20 Me), and 0.25 (s, 9 H, 3 SiMe).

Anal. Calc. for $C_{11}H_{18}O_3Si$ (226.3): C, 58.37; H, 8.02. Found: C, 58.35; H, 7.75.

(*b*) *Synthesis of (1,1-dimethylethyl)diphenylsilyloxy-3,5-dimethoxybenzene.*

This compound was synthesized from dimethoxyphenol and chloro(1,1-dimethylethyl)diphenylsilane according to a published general procedure[22], yield 53%, R_F (4:1, v/v, petroleum ether–ethyl acetate) 0.78; ^{1}H-n.m.r. (80 MHz, $CDCl_3$): δ 8.05–7.50 (m, 10 H, 2 C_6H_5), 6.00 (c.m., 3 H, H-2,4,6), 3.63 (s, 6 H, 2 OMe), and 1.10 (s, 9 H, CMe_3): m.s.: *m/e* 392 (M^+), 199 (100%).

(*c*) *Synthesis of* **4**. As described for the preparation of **2**, procedure (*a*) was applied to **1** (0.93 g, 1.35 mmol), 3,5-dimethoxytrimethylsilyloxybenzene (0.35 g, 1.55 mmol) in anhydrous dichloromethane (5 mL), and 0.25M diethyl ether·BF_3 in dichloromethane (4 mL, 1.00 mmol) to give, after 1 h, an oily residue that was purified on silica gel by flash chromatography (7:3, v/v, petroleum ether–ethyl acetate), yield 0.30 g (33%), colorless oil, $[\alpha]_{578}^{23}$ +33° (*c* 1, chloroform), R_F (4:1, v/v, toluene–ethyul acetate), 0.35; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 7.98 (s, 1 H, OH), 7.24–6.91 (m, 20 H, 4 C_6H_5), 6.07, 5.98 (2 d, 2 H, $J_{4,6}$ 1.3 Hz, H-4,6), 4.96–3.51 (m, 15 H, 4 CH_2, 7 sugar H), 3.68, and 3.59 (2 s, 6 H, 2 OMe); ^{13}C-n.m.r. (62.97 MHz, $CDCl_3$): δ 161.4, 158.6, 158.2 (3 s, 3 C, C-1,3,5), 138.8, 138.2, 138.0, 137.9 (4 s, 4 [C-1 (C_6 H_5)], 128.3–127.4 (C_6H_5), 104.9 (s, 1 C, C-2), 94.9, 91.4 (d, 2 C, C-4,6), 86.1, 81.6, 78.6, 75.5, 75.1, 75.0, 74.5, 73.4, 68.1)4 C_6H_5-*C*H_2, 6 sugar C), 55.6, and 55.2 (2 q, 2 C, 2 O*C*H_3).

Anal. Calc. for $C_{42}H_{44}O_8$ (676.8): C, 74.54; H, 6.55. Found: C, 74.28; H, 6.78.

(*d*) *Synthesis of* **5**. As described for the preparation of **2**, procedure (*a*) was applied to **1** (0.68 g, 1.01 mmol), (1,1-dimethylethyl)diphenylsilyloxy-3,5-dimethoxybenzene (0.68 g, 1.73 mmol) in anhydrous dichloromethane (15 mL), and 0.1M diethyl ether·BF_3 in dichloromethane (5 mL, 0.5 mmol) to give, after 2 h, an oily residue which was treated in oxolane (10 mL) with tetrabutylammonium fluoride trihydrate (0.80 g, 2.54 mmol) for 3 h. The mixture was purified on silica gel by flash chromatography (7:3, v/v, petroleum ether–ethyl acetate); yield 0.32 g (47%) of **5**, colorless oil [in addition to **4** (0.10 g, 15%)]; R_F (7:3, v/v, petroleum ether–ethyl acetate) 0.21; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 7.59–6.88 (m, 20 H, 4 C_6H_5), 6.19 (bs, 1 H, OH), 5.93, 5.86 (2.65, 2 H, H-2,6), 5.11–3.39 (m, 15 H, 4 CH_2, 7 sugar H), 3.62, and 3.56 (2 s, 6 H, 2 OMe).

Anal. Calc. for $C_{42}H_{44}O_8$ (676.8): C, 74.54; H, 6.55. Found: C, 74.36; H, 6.69.

*2-Acetoxy-4,6-dimethoxy-1-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)benzene* (**6**). — Compound **4** (0.21 g, 0.31 mmol) was dissolved in 1:1 (v/v) methanol–ethyl acetate (6 mL). After addition of Pd–C (80 mg), hydrogenation was monitored by t.l.c. (4:1, v/v, chloroform–methanol). After completion of the reaction, filtration and evaporation of the solvent gave a liquid residue which was dissolved in 1:1 acetic anhydride–2-methylpyridine (2 mL) at room temperature. After 17 h, the mixture was treated with water (50 mL), and then extracted three times with dichloromethane (20 mL). The organic layer was washed two times with M HCl (20 mL) and then evaporated. The oily residue was purified on silica gel by flash chromatography (2:3, v/v, petroleum ether–ethyl acetate). For analysis purposes,

the material was again purified on silica gel by elevated pressure chromatography with the same solvent system; yield 0.14 g (84%), amorphous solid, $[\alpha]_{578}^{23}$ −43° (*c* 1, chloroform), R_F (2:3, v/v, petroleum ether–ethyl acetate) 0.53; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 6.31, 6.22 (2 d, 2 H, $J_{4,6}$ 2.5 Hz, H-4,6), 5.70–5.65 (m, 1 H, H-2′), 5.30–5.10 (m, 2 H, H-3′,4′), 4.85 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1′), 4.40–4.00 (m, 2 H, H-6′,6″), 3.70 (cm, 1 H, H-5′), 3.81, 3.76 (2 s, 6 H, 2 OMe), 2.34 (s, 3 H, $COCH_3$), 2.04, 2.02, 1.99, and 1.75 (4 s, 12 H, 4 $COCH_3$).

Anal. Calc. for $C_{24}H_{30}O_{13}$ (526.5): C, 54.75; H, 5.74. Found: C, 54.77; H, 5.68.

*Methyl 3-[2,4,6-trimethoxy-3-(2,3,4,6-tetra-*O*-benzyl-β-*D*-glucopyranosyl)-phenyl]propionate* (**7**). — (*a*) *Synthesis of methyl 3-(2,4,6-trimethoxyphenyl)propionate*. Methyl 2,4,6-trimethoxycinnamate[23] (0.70 g, 2.77 mmol) was dissolved in methanol (30 mL) and hydrogenated after addition of PtO_2 (150 mg). After completion of the reaction, filtration and evaporation gave a solid residue that was purified on silica gel by elevated pressure chromatography (4:1, v/v, petroleum ether–ethyl acetate); yield 0.43 g (61%), amorphous solid, R_F (4:1, v/v, petroleum ether–ethyl acetate) 0.58; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 6.11 (s, 2 H, H-3,5), 3.79 (s, 3 H, OMe), 3.78 (s, 6 H, 2 OMe), 3.66 (s, 3 H, CO_2Me), 2.99–2.82 (m, 2 H, β-CH_2), and 2.53–2.34 (m, 2 H, α-CH_2).

Anal. Calc. for $C_{13}H_{18}O_5$ (254.3): C, 61.41; H, 7.14. Found: C, 61.26; H, 7.16.

(*b*) *Synthesis of* **7**. As described for the preparation of **2**, procedure (*a*) was applied to **1** (0.91 g, 1.33 mmol), methyl 3-(2,4,6-trimethoxyphenyl)-propionate (0.30 g, 1.18 mmol) in anhydrous dichloromethane (10 mL), and 0.1M diethyl ether·BF_3 in dichloromethane (8 mL, 0.80 mmol) to give an oily residue that was purified on silica gel by flash chromatography (7:3, v/v, petroleum ether–ethyl acetate); yield 0.12 g of unreacted propionate and 0.44 g of **3** (80%, relative to used **1**), colorless oil, R_F (7:3, v/v, petroleum ether–ethyl acetate) 0.53; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 7.34–6.83 (m, 20 H, 4 C_6H_5), 6.27, 6.22 (2s, 1 H, H-5), 4.98–4.43 (m, 9 H, 4 C_6H_5–CH_2, 1 sugar H), 4.14, 4.02 (2 d, 1 H, $J_{1',2'}$ 10.6 Hz, H-1′), 3.91–3.55 (m, 5 H, 5 sugar H), 3.83, 3.82, 3.81, 3.77, 3.73, 3.70, 3.69, 3.62 (6 s, 12 H, 4 OMe), 2.96–2.78 (m, 2 H, β-CH_2), and 2.58–2.41 (m, 2 H, α-CH_2).

This material was directly transformed into **8**.

*Methyl 3-[2,3,6-trimethoxy-3-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl]propionate* (**8**). — This compound was obtained from **7** (0.23 g, 0.30 mmol) as described for the preparation of **6**; yield 0.13 g (74%) colorless oil; R_F (2:3, v/v, petroleum ether–ethyl acetate) 0.49; ^{1}H-n.m.r. [250 MHz, ($^2H_6$)Me_2SO, 130°]: δ 6.42 (s, 1 H, H-5), 5.76 (dd, 1 H, $J_{1',2'}$ 9.8, $J_{2',3'}$ 9.6 Hz, H-2′), 5.21 (dd, 1 H, $J_{2',3'}$ 9.6, $J_{3',4'}$ 9.3 Hz, H-3′), 4.99 (dd, 1 H, $J_{3',4'}$ 9.3, $J_{4',5'}$ 9.8 Hz, H-4′), 4.89 (d, 1 H, $J_{1',2'}$ 9.8 Hz, H-1′), 4.10 (cm, 2 H, H-6′,6″), 3.93–3.86 (m, 1 H, H-5′), 3.80, 3.72, 3.59 (3 s, 12 H, 4 OMe), 2.79 (cm, 2 H, α-CH_2), 2.43 (cm, 2 H, β-CH_2), 1.99, 1.95, 1.91, and 1.66 (4 s, 12 H, 4 $COCH_3$).

Anal. Calc. for $C_{27}H_{36}O_{14}$ (584.6): C, 55.48; H, 6.21. Found: C, 55.27; H, 6.30.

2-[2,4,6-Trimethoxy-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)phenyl]-1-propene (**9**) *and 3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-2-(2,4,6-trimethoxyphenyl)-1-propene* (**12**). — As described for the preparation of **2**, procedure (*a*) applied to **1** (0.53 g, 0.77 mmol), 2-(2,4,6-trimethoxyphenyl)-1-propene[24] (0.15 g, 0.72 mmol) in anhydrous dichloromethane (8 mL), and 0.56M diethyl ether · $ZnCl_2$ in dichloromethane (6 mL, 3.36 mmol) gave, after 1 h, and oily residue that was purified on silica gel by flash chromatography (4:1 v/v, petroleum ether–ethyl acetate). Separation of the isomers was performed by elevated pressure chromatography on silica gel (19:1, v/v, toluene–ethyl acetate) to give **9** (0.21 g, 39%), **6**, and **12** (0.21 g, 39%), colorless oils.

Compound **9**. $[\alpha]_{578}^{23}$ +18° (*c* 1, chloroform), R_F (19:1, v/v, toluene–ethyl acetate)0.14; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 7.36–6.97 (m, 20 H, 4 C_6H_5), 6.27 (s, 1 H, H-5), 5.84 (d, 1 H, $J_{1',2'}$ 7.3 Hz, H-1′), 5.32, 4.94 (2 cm, 2 H, $=CH_2$), 4.81–4.26 (m, 8 H, 4 $C_6H_5CH_2$), 4.05 (dd, 1 H, $J_{1',2'}$ 7.3, $J_{2',3'}$ 7.3 Hz), 4.03–3.95 (m, 1 H, H-5′), 3.82 (s, 3 H, OMe), 3.72 (s, 6 H, 2 OMe), 3.80–3.62 (m, 4 H, H-3′,4′,6′,6″), and 2.05 (s, 3 H, C–CH_3).

Anal. Calc. for $C_{46}H_{50}O_8$ (730.9): C, 75.59; H, 6.90. Found: C, 75.38; H, 6.99.

Compound **12**. $[\alpha]_{578}^{23}$ +38° (*c* 1, chloroform), R_F (19:1, v/v, toluene–ethyl acetate) 0.15; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 7.34–7.12 (m, 20 H, 4 C_6H_5), 6.11 (s, 2 H, H-3,5), 5.41 [cm, 1 H, =CH (*Z*)], 4.99 [(d, 1 H, *J* 1.8 Hz, =CH (*E*)], 4.93–4.44 (m, 8 H, 4 C_6H_5–CH_2), 4.34–4.22 (m, 1 H, H-1′), 3.80 (s, 3 H, OMe), 3.70 (s, 6 H, 2 OMe), 3.78–3.49 (m, 6 H, 6 sugar H), and 2.89–2.68 (m, 2 H, C–CH_2–C).

Anal. Calc. for $C_{46}H_{50}O_8$ (730.9): C, 75.59; H, 6.90. Found: C, 75.39; H, 7.03.

2-Hydroxy-4,6-dimethoxy-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)acetophenone (**10**). — As described for the preparation of **2**, procedure (*a*) applied to **1** (0.59 g, 0.85 mmol), 2-hydroxy-4,6-dimethoxyacetophenone[25] (0.17 g, 0.89 mmol) in anhydrous dichloromethane (10 mL), and $ZnCl_2$ (0.24 g, 1.75 mmol) gave, after 3 h, an oily residue that was purified on silica gel by flash chromatography (3:2, v/v, petroleum ether–ethyl acetate) and then on silica gel by elevated pressure chromatography (9:1, v/v, toluene–acetone); yield 0.09 g (17%), colorless oil, $[\alpha]_{578}^{23}$ +16° (*c* 1, chloroform); R_F (3:2, v/v, petroleum ether–ethyl acetate) 0.41; ^{1}H-n.m.r. (80 MHz, $CDCl_3$): δ 14.30 (bs, 1 H, OH), 6.03 (s, 1 H, H-6), 6.01 (d, 1 H, $J_{1',2'}$ 7 Hz, H-1′), 5.00–3.70 (m, 14 H, 4 C_6H_5–CH_2, 6 sugar H), 3.94, 3.88 (2 s, 6 H, 2 OMe), and 2.65 (s, 3 H, $COCH_3$).

Anal. Calc. for $C_{44}H_{47}O_9$ (719.9): C, 73.42; H, 6.58. Found: C, 73.63; H, 6.55.

1,2,3-Trimethoxy-4-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)benzene (**13**). — As described for the preparation of **2**, procedure (*a*) applied to **1** (0.67 g, 0.97 mmol), 1,2,3-trimethoxybenzene[26] (0.33 g, 1.94 mmol) in anhydrous dichloromethane (5 mL), and $ZnCl_2$ (0.35 g, 2.57 mmol) gave, after 6 h, an oily residue that

was purified on silica gel by flash chromatography (1:1, v/v, petroleum ether–diethyl acetate); yield 0.11 g (17%), colorless oil, R_F (1:1, v/v, petroleum ether–diethyl acetate) 0.37; ^{1}H-n.m.r. (80 MHz, $CDCl_3$): δ 7.75–7.20 (m, 20 H, 4 C_6H_5), 6.90–6.70 (m, 2 H, H-5,6), 5.86 (d, 1 H, $J_{1',2'}$ 4 Hz, H-1'), 5.18–3.75 (m, 14 H, 4 C_6H_5–CH_2, and 6 sugar H), and 3.93 (bs, 9 H, 3 OMe).

Anal. Calc. for $C_{43}H_{46}O_8$ (690.8): C, 74.76; H, 6.71. Found: C, 74.52; H, 6.83.

*3,4,5-Trimethoxy-2-(2,3,4,6-tetra-*O*-benzyl-β-* (**14**) *and -α-*D*-glucopyranosyl)-toluene*. — As described for the preparation of **2**, procedure (*a*) applied to **11** (0.87 g, 0.95 mmol), 3,4,5-trimethoxytoluene (0.30 mL, 1.78 mmol) in anhydrous dichloromethane (10 mL), and 0.1M diethyl ether·BF_3 in dichloromethane (10 mL, 1.0 mmol) gave, after 1 h, an oily residue that was purified on silica gel by flash chromatography, and then by elevated pressure chromatography (4:1, v/v, petroleum ether–ethyl acetate), **14** (0.28 g, 47%) and its α-D anomer (20 mg, 3%).

Compound **14**. Colorless oil, rotamers, R_F (4:1, v/v, petroleum ether–ethyl acetate) 0.39; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): **10** δ 7.32–6.92 (m, 20 H, 4 C_6H_5), 6.50, 6.46 (2 s, 1 H, H-6), 4.95–4.43 (m, 8 H, 4 C_6H_5–CH_2), 4.13–3.74 (m, 7 H, 7 sugar H), 3.85, 3.83, 3.81, 3.80 (4s, 9 H, 3 OMe), 2.47–2.26 (3s, 3 H, C–CH_3).

Anal. Calc. for $C_{44}H_{48}O_8$ (704.9): C, 74.98; H, 6.86. Found: C, 74.46; H, 6.92.

*α-*D *Anomer of* **14**. Colorless oil, $[\alpha]_{578}^{23}$ +23° (*c* 1, chloroform), R_F (4:1, v/v, petroleum ether–ethyl acetate) 0.46; ^{1}H-n.m.r. (250 MHz, $CDCl_3$):δ 7.31–7.00 (m, 20 H, 4 C_6H_5), 6.48 (s, 1 H, H-6), 5.53 (d, 1 H, $J_{1',2'}$ 3.2 Hz, H-1'), 4.72–4.16 (m, 8 H, 4 C_6H_5–CH_2), 4.00–3.71 (m, 6 H, 6 sugar H), 3.86, 3.78, 3.66 (3 s, 9 H, 3 OMe), 2.60 (s, 3 H, C–CH_3).

Anal. Calc. for $C_{44}H_{48}O_8$ (704.9): C, 74.98, H, 6.86. Found: C, 74.87; H, 7.00.

*3,4,5-Trimethoxy-2-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)toluene* (**15**). — As described for the preparation of compound **6**, **14** (0.28 g, 0.40 mmol) gave **15** (0.18 g, 88%), colorless oil as rotamers, $[\alpha]_{578}^{25}$ −14° (*c* 1, chloroform), R_F (3:2, v/v, petroleum ether–ethyl acetate) 0.24; ^{1}H-n.m.r. [250 MHz, ($^2H_6$)Me_2SO, 100°]: δ 6.54 (s, 1 H, H-6), 5.51 (dd, 1 H, $J_{1',2'}$ 9.5, $J_{2',3'}$ 9.5 Hz, H-2'), 5.27 (dd, 1 H, $J_{2',3'}$ 9.5, $J_{3,',4'}$ 9.5 Hz, H-3'), 5.04 (dd, 1 H, $J_{3',4'}$ 9.5, $J_{4',5'}$ 9.8 Hz, H-4'), 4.93 (d, 1 H, $J_{1',2'}$ 9.5 Hz, H-1'), 4.14 (cm, 2 H, H-6',6''), 3.99–3.96 (m, 1 H, H-5'), 3.80, 3.77, 3.71 (3 s, 9 H, 3 OMe), 2.35 (s, 3 H, C–CH_3), 2.00, 1.98, 1.92, and 1.70 (4 s, 12 H, 4 $COCH_3$).

Anal. Calc. for $C_{24}H_{28}O_{12}$ (508.5): C, 56.69; H, 6.55. Found: C, 56.29; H, 6.32.

*1,2,4-Trimethoxy-5-(2,3,4,6-tetra-*O*-benzyl-β-*D*-glucopyranosyl)benzene* (**16**). — As described for the preparation of **2**, procedure (*a*) applied to **1** (0.60 g, 0.87 mmol), 1,2,4-trimethoxybenzene (0.13 mL, 0.77 mmol) in anhydrous dichloromethane (10 mL), and $ZnCl_2$ (0.01 g, 0.70 mmol) gave, after 4 h an oily residue that was purified on silica gel by flash chromatography and elevated pressure

chromatography (3:1, v/v, petroleum ether–ethyl acetate); yield 0.25 g (47%), colorless oil $[\alpha]_{578}^{23}$ +4.5° (*c* 1, chloroform); R_F (7:3, v/v, petroleum ether–ethyl acetate) 0.35; ^{1}H-n.m.r. (80 MHz, $CDCl_3$): δ 7.75–7.10 (m, 21 H, 4 C_6H_5, H-6), 6.70 (s, 1 H, H-3), 5.20–3.60 (m, 15 H, 4 C_6H_5–CH_2, 7 sugar H), 3.95, 3.83, and 3.80 (3 s, 9 H, 3 OMe).

Anal. Calc. for $C_{43}H_{46}O_8$ (690.8): C, 74.76; H, 6.71. Found: C, 74.75; H, 6.85.

*1,2,4-Trimethoxy-5-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)benzene* (**17**). — As described for the preparation of compound **6, 16** (0.14 g, 0.20 mmol) gave **17** (66 mg, 73%), colorless foam, $[\alpha]_{578}^{23}$ −18° (*c* 1, chloroform), R_F (3:2, v/v, petroleum ether–ethyl acetate) 0.46; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 6.88 (s, 1 H, H-6), 6.49 (s, 1 H, H-3), 5.50–5.20 (m, 3 H, H-2′,3′,4′), 4.90 (d, 1 H, $J_{1',2'}$ 9.8 Hz, H-1′), 4.32–4.08 (m, 2 H, H-6′,6″), 3.90–3.75 (m, 1 H, H-5′), 3.89, 3.85, 3.82 (3 s, 9 H, 3 OMe), 2.07, 2.06, 2.01 (3 s, 9 H, 3 $COCH_3$), and 1.79 (s, 3 H, CH_3CO).

Anal. Calc. for $C_{23}H_{30}O_{12}$ (498.5): C, 55.42; H, 6.07. Found: C, 55.48; H, 6.13.

*2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-*D*-glucopyranose* (**18**). — A solution of 3,4,6-tri-*O*-acetyl-1,2-*O*-(1-methoxyethylidene)-D-glucose orthoacetate[17] (31.7 g, 94.14 mmol) in anhydrous methanol (100 mL) was treated at 0° with anhydrous NH_3 gas. After 2 h, the mixture was evaporated to complete dryness. The residue was dissolved in anhydrous *N,N*-dimethylformamide (250 mL). To the solution at 0° and under a N_2 atmosphere, NaH (11.60 g, 483.3 mmol) was added. When the formation of H_2 had ceased, benzyl bromide (48.5 mL, 483.3 mmol) was added slowly with strong stirring. In order to complete the benzylation, additional NaH (4.0 g, 0.167 mol) and benzyl bromide (20 mL, 0.2 mol) were added after 12 h. Slow addition of methanol (20 mL) and then water (500 mL) ended the reaction. The organic material was extracted with chloroform (3 × 100 mL), the organic phase dried ($MgSO_4$), and evaporated. The oily residue was purified by chromatography on silica gel, which had been activated by treatment with HNO_2 (7:3, v/v, petroleum ether–ethyl acetate). This material was pure enough for further reactions; yield 30.25 g (74%), viscous oil. Addition of 7:2 (v/v) petroleum ether–ethyl acetate gave the α-D anomer as crystalline material, m.p. 124–126°, $[\alpha]_{578}^{23}$ +64° (*c* 1, chloroform); R_F (7:3, v/v, petroleum ether–ethyl acetate) 0.32; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 7.36–7.09 (m, 15 H, 3 C_6H_5), 5.40 (cm, 1 H, H-1), 4.88 (dd, 1 H, $J_{1,2}$ 2.7, $J_{2,3}$ 10.7, H-2), 4.83–4.47 (m, 6 H, 3 C_6H_5–CH_2), 4.11–4.01 (m, 2 H, H-3,4), 3.72–3.58 (m, 3 H, H-5,6,6′), 3.18 (bd, 1 H, OH), and 2.03 (s, 3 H, $COCH_3$).

Anal. Calc. for $C_{29}H_{31}O_7$ (491.6): C, 70.86; H, 6.36. Found: C, 70.61; H, 6.49.

*3,4,6-Tri-*O*-benzyl-*D*-glucopyranose* (**19**). — A solution of **18** (10.0 g, 20.34 mmol) in anhydrous methanol (200 mL) was treated at 0° with anhydrous NH_3 gas for 4 h and, after 12 h at room temperature, the solvent was evaporated and the residue chromatographed on silica gel (1:1, v/v, petroleum ether–ethyl acetate); yield 1.73 g (84%), amorphous solid, R_F (3:2, v/v, petroleum ether–ethyl acetate) 0.13; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 7.36–7.08 (m, 15 H, 3 C_6H_5), 5.36 (bs, 0.5 H,

H-1), 5.20 (cm, 0.5 H, H-1α), 4.93–4.75 (m, 3 H, 1.5 C_6H_5–CH_2), 4.64 (bs, 0.5 H, H-1), 4.57–4.41 (m, 3.5 H, 1.5 C_6H_5–CH_2, H-1β), 4.04–3.41 (m, 6 H, 6 sugar H), and 2.76 (d, 0.5 H, *J* 6.4 Hz, H-2α).

Anal. Calc. for $C_{27}H_{30}O_6$ (450.5): C, 71.98; H, 6.71. Found: C, 71.84; H, 6.75.

3,4,6-Tri-O-benzyl-1,2-di-O-(3,4,5-trimethoxybenzoyl)-α,β-D-glucopyranose (**20**). — To a solution of **19** (6.74 g, 14.96 mmol) and 2-methylpyridine (10 mL, 102.76 mmol) in anhydrous dichloromethane (5 mL) and toluene (15 mL) was added, at 0°, 3,4,5-trimethoxybenzoyl chloride[27] (10.13 g, 49.95 mmol) dissolved in toluene (10 mL). After 2 h, the mixture was poured onto ice–water (150 mL) and then extracted with dichloromethane (3 × 40 mL). The organic phase was washed with M NaOH (50 mL) and M HCl (50 mL), dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel (3:2, v/v, petroleum ether–ethyl acetate); yield 9.67 g (77%), colorless oil. The anomers were separated by elevated pressure chromatography with the same solvent system.

α-D Anomer. $[\alpha]_{578}^{23}$ +137° (*c* 1, chloroform), R_F t.l.c. (3:2, v/v, petroleum ether–ethyl acetate) 0.62; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 7.38–7.09 (m, 19 H, aryl H), 6.62 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 5.47 (dd, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 9.9 Hz, H-2), 4.91–4.52 (m, 6 H, 3 C_6H_5–CH_2), 4.19 (dd, 1 H, $J_{2,3}$ 9.9, $J_{3,4}$ 8.8 Hz, H-3), 4.03–3.52 (m, 4 H, H-4,5,6,6′), 3.91, 3.86, 3.85 (3 s, 12 H, 4 OMe), and 3.64 (s, 6 H, 2 OMe).

Anal. Calc. for $C_{47}H_{50}O_{14}$ (838.9): C, 67.29; H, 6.01. Found: C, 67.35; H, 6.24.

β-D Anomer. $[\alpha]_{578}^{23}$ +1.1° (*c* 1, chloroform), R_F (3:2, v/v, petroleum ether–ethyl acetate) 0.51; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 7.34–7.25 (m, 19 H, aryl H), 5.92 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1), 5.59 (dd, 1 H, $J_{1,2}$ 8.2 Hz, $J_{2,3}$ 8.2 Hz, H-2), 4.87–4.50 (m, 6 H, 3 C_6H_5–CH_2), 4.00–3.67 (m, 5 H, 5 sugar H), 3.88 (s, 12 H, 4 OMe), and 3.84 (s, 6 H, 2 OMe).

Anal. Calc. for $C_{47}H_{50}O_{14}$ (838.9): C, 67.29; H, 6.01. Found: C, 67.38; H, 6.14.

3,4,6-Tri-O-benzyl-2-O-(3,4,6-trimethoxybenzoyl)-D-glucopyranose (**21**). — In analogy to the procedure of Excoffier *et al.*[28], a solution of **20** (4.23 g, 5.14 mmol) and hydrazine acetate (1.10 g, 11.82 mmol) in anhydrous *N,N*-dimethylformamide (20 mL) was warmed to 55° for 4 h and kept at room temperature for 2 h. Then ethyl acetate (70 mL) was added and the mixture poured on a saturated NaCl solution (30 mL). The organic phase was extracted with ethyl acetate (2 × 30 mL), dried, and the solvent evaporated. The solid residue was crystallized from ethanol. The mother liquor was purified by chromatography on silica gel (3:2, v/v, petroleum ether–ethyl acetate); yield 2.38 g (72%), colorless crystals, m.p. 167°; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 7.35–7.14 (m, 17 H, aryl H), 5.58 (m, 1 H, H-1), 5.09 (dd, 1 H, $J_{1,2}$ 2.3, $J_{2,3}$ 9.8 Hz, H-2), 4.85–4.50 (m, 6 H, 3 C_6H_5–CH_2), 4.23 (dd, 1 H, $J_{2,3}$ 9.8, $J_{3,4}$ 9.2 Hz, H-3), 4.15 (m, 1 H, H-5), 3.90 (s, 3 H, OMe), 3.83 (s, 6 H, 2 OMe), 3.74–3.66 (m, 3 H, H-4,6,6′), and 3.05 (m, 1 H, OH).

Anal. Calc. for $C_{37}H_{40}O_{10}$ (644.7): C, 68.93; H, 6.25. Found: C, 68.74; H, 6.44.

3,4,6-Tri-O-benzyl-2-O-(3,4,5-trimethoxybenzoyl)-α- and -β-D-glucopyranosyl trichloroacetimidate (**22**). — To a solution of **21** (0.38 g, 0.59 mmol) and trichloroacetonitrile (1 mL, 9.97 mmol) in anhydrous dichloromethane (25 mL) was added, at room temperature, anhydrous K_2CO_3 (4.0 g). The mixture was stirred for 19 h and then NaH (20 mg) added. After 3 h, the solid material was filtered off and the solvent evaporated. The oily residue was purified by flash chromatography on silica gel (7:3, v/v, petroleum ether–ethyl acetate) (an analytical sample was purified by elevated pressure chromatography on silica gel with the same solvent system) to give 0.38 g (81%) of α-D anomer and 0.08 g (17%) of β-D anomer.

α-D-*Anomer*. $[\alpha]_{578}^{23}$ +8° (*c* 1, chloroform), R_F (7:3, v/v, petroleum ether–ethyl acetate) 0.71; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 8.53 (s, 1 H, NH), 7.37–7.16 (m, 17 H, aryl H), 6.65 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 5.43 (dd, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 10.2 Hz, H-2), 4.90–4.51 (m, 6 H, 3 C_6H_5–CH_2), 4.26 (dd, 1 H, $J_{2,3}$ 10.2, $J_{3,4}$ 10.2 Hz, H-3), 4.09–3.76 (m, 4 H, 4 sugar H), 3.92 (s, 3 H, OMe), and 3.84 (s, 6 H, 2 OMe).

Anal. Calc. for $C_{39}H_{40}Cl_3NO_{10}$ (789.1): C, 59.36; H, 5.11; N, 1.78. Found: C, 58.94; H, 5.35; N, 1.50.

β-D *Anomer*. $[\alpha]_{578}^{23}$ +64° (*c* 1, chloroform), R_F (7:3, v/v, petroleum ether–ethyl acetate) 0.51; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 8.61 (s, 1 H, NH), 7.37–7.12 (m, 17 H, aryl H), 5.95 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1), 5.54 (cm, 1 H, H-5), 4.86–4.54 (m, 6 H, 3 C_6H_5–CH_2), 3.94–3.75 (m, 5 H, 5 sugar H), 3.91 (s, 3 H, OMe), and 3.86 (s, 6 H, 2 OMe).

(3R,4R,4aR,10bS)-3,4-Diacetoxy-2-acetoxymethyltetrahydropyrano[5,6-c]-3,4-dihydroisocoumarin (**24**). — As described for the preparation of **2**, procedure (*a*) applied to the α-D anomer of **22** (0.24 g, 0.30 mmol) in anhydrous toluene (30 mL) and 0.1M diethyl ether·BF_3 in anhydrous dichloromethane (5 mL, 0.5 mmol) gave, after 2 h, an oily residue. This was purified by flash chromatography on silica gel (3:2, v/v, petroleum ether–ethyl acetate) to give a material (0.20 g) that contained **23** and **26**. As described for compound **6**, this material was transformed into compounds **24** and **27**, which were separated by flash chromatography on silica gel (2:3, v/v, petroleum ether–ethyl acetate) to give **24** (50 mg, 35%) and **27** (26 mg, 20%). Compound **24** showed m.p. 212° (ethanol), $[\alpha]_{578}^{23}$ −9.1° (*c* 1, chloroform), R_F (2:3, v/v, petroleum ether–ethyl acetate) 0.26; ^{1}H-n.m.r. (400 MHz, CD_3CN): δ 7.26 (s, 1 H, H-7), 5.42 (dd, 1 H, $J_{3,4}$ 9.5, $J_{4,4a}$ 9.5 Hz, H-4), 5.10 (d, 1 H, $J_{5,10b}$ 7.8 Hz, H-10b), 5.04 and 4.98 (m, 2 H, H-3,4a), 4.12–4.05 (m, 2 H, CH_AH_BOAc), 3.86–3.78 (m, 1 H, H-2), 3.86 (s, 6 H, 2 OMe), 3.80 (s, 3 H, OMe), 1.93, 1.89, 1.84 (3 s, 9 H, 3 $COCH_3$); [250 MHz; 9:1, v/v, ($^2H_6$)acetone–$CDCl_3$] δ 7.28 (s, 1 H, H-7), 5.44 (dd, 1 H, $J_{3,4}$ 9.5, $J_{4,4a}$ 9.5 Hz, H-4), 5.28 (d, 1 H, $J_{4a,10b}$ 7.9 Hz, H-10b), 5.10 (dd, 1 H, $J_{4a,10b}$ 7.9, $J_{4,4a}$ 9.5 Hz, H-4a), 5.06 (dd, 1 H, $J_{2,3}$ 9.5, $J_{3,4}$ 9.5 Hz, H-3), 4.19 (dd, 1 H, J_{2,H_A} 5.2, J_{H_A,H_B} 12.8 Hz, CH_AH_BOAc), 3.98 (dd, 1 H, J_{2,H_B} <1, J_{H_A,H_B} 12.8 Hz, CH_AH_BOAc), 3.89 (s, 6 H, 1 OMe), 3.83 (s, 3 H, OMe), 3.87–3.80 (m, 1 H, H-2), 1.98, 1.90, and 1.87 (3 s, 9 H, 3 $COCH_3$); ^{13}C-n.m.r. (100 MHz, $CDCl_3$): δ 170.2, 170.0, 169.8 (3 s, 3 C, 3 $COCH_3$), 164.2 (s, 1 C, aryl *C*O), 152.8 (s, 2 C, C-8,10), 142.5 (s, 1 C, C-9), 124.1 (s, 2 C, C-6a,10a), 107.2 (d, 1 C, C-7), 96.9, 72.2, 72.1, 71.3, 69.1 (5 d, 5 C, 5 pyranose C), 61.7 (t, CH_2OAc), 60.7

(q, 1 C, OMe-4), 56.1 (q, 2 C, OMe-3,4), and 20.4 (q, 3 C, 3 CO–CH_3); m.s.: *m/z* 483 ($M + H^+$) and 195 (100%).

Anal. Calc. for $C_{22}H_{26}O_{12} \cdot 0.5\ H_2O$ (491.446): C, 53.76; H, 5.54. Found: C, 53.62; H, 5.43.

3,4,6-Tri-O-benzyl-1-N-(trichloroacetyl)-2-O-(3,4,5-trimethoxybenzoyl)-β-D-glucopyranosylamine (**25**). — As described for the preparation of **2**, procedure (*a*) applied to the α-D anomer of **22** (1.06 g, 1.34 mmol) in anhydrous hexane–dichloromethane (12 mL, 5:1, v/v) and trifluoromethanesulfonic acid (0.50 mL, saturated solution) gave, after 3 h, and oily residue that was purified by flash chromatography on silica gel (7:3, v/v, petroleum ether–ethyl acetate); yield 0.71 g (67%) colorless oil, $[\alpha]_{578}^{23}$ +82° (*c* 1, chloroform), R_F (7:3, v/v, petroleum ether–ethyl acetate) 0.45; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 7.62 (d, 1 H, *J* 7.6 Hz, NH), 7.62–7.17 (m, 17 H, aryl H), 5.23 (cm, 2 H, H-1,2), 4.86–4.50 (m, 6 H, 3 C_6H_5–CH_2), 3.91 (s, 3 H, OMe), 3.86 (s, 6 H, 2 OMe), and 4.01–3.65 (m, 5 H, 5 sugar H).

Anal. Calc. for $C_{39}H_{40}Cl_3NO_{10}$ (789.1): C, 59.36; H, 5.11; Cl, 13.48; N, 1.78. Found: C, 58.96; H, 5.06; Cl, 13.09; N, 1.75.

1,6-Anhydro-3,4-di-O-benzyl- (**26**) *and 3,4-di-O-acetyl-2-O-(3,4,5-trimethoxybenzoyl)-β-D-glucopyranose* (**27**). — As described for the preparation of **2**, procedure (*a*) applied to the β-D anomer of **22** (0.11 g, 0.14 mmol) in anhydrous dichloromethane (10 mL) and 0.56M diethyl ether · $ZnCl_2$ in dichloromethane (2 mL, 1.12 mmol) gave, after 4 h, an oily residue. This was purified by flash chromatography and elevated pressure chromatography on silica gel (7:3, v/v, petroleum ether–ethyl acetate) to give **26** (20 mg, 27%) and **21** (50 mg, 55%).

Compound **26**. Colorless oil $[\alpha]_{578}^{23}$ +17.5° (*c* 1, chloroform); R_F (7:3, v/v, petroleum ether–ethyl acetate) 0.33; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 7.36–7.25 (m, 12 H, aryl H), 5.58 (cm, 1 H, H-1), 5.00 (cm, 1 H, H-2), 4.85 (d, 1 H, *J* 12.0 Hz, C_6H_5–C*H*-4), 4.71–4.70 (m, 1 H, H-5), 4.61 (d, 1 H, *J* 12.0 Hz, C_6H_5–C*H*-4), 4.50 (s, 2 H, C_6H_5–CH_2-3), 4.16–4.13 (m, 1 H, sugar H), 3.87–3.45 (m, 2 H, 2 sugar H), 3.91 (s, 3 H, OMe), and 3.80 (s, 6 H, 2 OMe).

Anal. Calc. for $C_{30}H_{32}O_9$ (536.6): C, 67.15; H, 6.01. Found: C, 67.38; H, 6.12.

Compound **26** was transformed into compound **27** as described for the preparation of compound **24**; yield 74%, colorless foam, $[\alpha]_{578}^{23}$ +50° (*c* 1, chloroform); R_F (2:3, v/v, petroleum ether–ethyl acetate) 0.46; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 7.35 (s, 2 H, aryl H), 5.58 (cm, 1 H, H-1), 5.08 (cm, 1 H, H-3), 4.82 (cm, 1 H, H-2), 4.71 (cm, 1 H, H-4), 4.67 (cm, 1 H, H-5), 4.16 (dd, 1 H, $J_{5,6} < 1$, $J_{6,6'}$ 7.3 Hz, H-6), 3.92 (s, 9 H, 3 OMe), 3.86 (dd, 1 H, $J_{5,6'}$ 5.5, $J_{6,6'}$ 7.3 Hz, H-6′), 2.16, and 2.13 (2 s, 6 H, 2 $COCH_3$).

Anal. Calc. for $C_{20}H_{24}O_{11}$ (440.4): C, 54.55; H, 5.49. Found: C, 54.47; H, 5.50.

1,3-Dimethoxy-4-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)benzene[11,29] (**29**). — As described for the preparation of **2**, procedure (*a*) applied to **1** (0.85 g, 1.2 mmol), 1,3-dimethoxybenzene (0.17 g, 1.2 mmol) in anhydrous dichloro-

methane (20 mL), and 0.5M diethyl ether·BF_3 in dichloromethane (0.5 mL, 0.25 mmol) gave an oily residue that was purified by elevated pressure chromatography on silica gel (3:2, v/v, petroleum ether–diethyl acetate); yield 0.60 g, (76%), colorless crystals, $[\alpha]_{578}^{23}$ +15.6° (*c* 1, chloroform); ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 7.40–6.85 (m, 21 H, 4 C_6H_5, H-5), 6.57–6.45 (m, 2 H, H-2,6), 4.99–3.92 (m, 8 H, 4 CH_2) 3.81 (s, 3 H, OMe), 3.74 (s, 3 H, OMe), and 3.82–3.52 (m, 6 H, 6 sugar H).

Anal. Calc. for $C_{42}H_{44}O_7$ (660.8): C, 76.34; H, 6.71. Found: C, 76.26; H, 6.70.

*1,3-Dihydroxy-4-(2,3,4,6-tetra-*O*-benzyl-β-*D*-glucopyranosyl)benzene* (**30**). — As described for the preparation of **2**, procedure (*a*) applied to **1** (2.0 g, 2.9 mmol), 1,3-bis(trimethylsilyloxy)benzene (0.75 g, 2.9 mmol) in anhydrous dichloromethane (30 mL), and 0.5M diethylether·BF_3 in dichloromethane (2 mL, 1.0 mmol) gave an oily residue that was treated with 0.2N H_2SO_4 (30 mL) at reflux for 8 h to remove the silyl groups. This mixture was made neutral, concentrated, the organic material extracted with dichloromethane (2 × 50 mL), and the solvent evaporated. Purification by elevated pressure chromatography on silica gel (4:1, v/v, petroleum ether–ethyl acetate) yielded a colorless oil (1.01 g, 54%), R_F (4:1, v/v, petroleum ether–ethyl acetate) 0.23; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 7.40–7.05 (m, 21 H, 4 C_6H_5, H-5), 6.70–6.46 (m, 2 H, H-2,6), 5.18–4.55 (m, 9 H, 4 CH_2, H-1′), and 3.97–3.58 (m, 6 H, 6 sugar H).

Anal. Calc. for $C_{40}H_{40}O_7$ (632.7): C, 75.93; H, 6.37. Found: C, 75.75; H, 6.29.

1-Hydroxymethyl-3,5-dimethoxy-2- (**32**) *and -4-(2,3,4,6-tetra-*O*-benzyl-β-*D*-glucopyranosyl)benzene* (**35**). — (*a*) *Synthesis of (1,1-dimethylethyl)diphenylsilyl 3,5-dimethoxybenzyl ether*. This compound was prepared according to a general procedure[22] from 3,5-dimethoxybenzyl alcohol; yield 63%, slightly yellow oil; ^{1}H-n.m.r. (80 MHz, $CDCl_3$): δ 7.72–7.25 (m, 10 H, 2 C_6H_5), 6.51–6.31 (m, 3 H, H-2,4,6), 4.72 (s, 2 H, CH_2), 3.76 (s, 6 H, 2 OMe), and 1.10 (s, 9 H, CMe_3); m.s.: *m/z* 349 (M^+ − *tert.*butyl), 151 (100%).

(*b*) *Synthesis of* **32** *and* **35**. As described for the preparation of **2**, procedure (*a*) applied to **1** (0.94 g, 1.37 mmol), (1,1-dimethylethyl)diphenylsilyl 3,5-dimethoxybenzyl ether (0.64 g, 1.57 mmol) in anhydrous dichloromethane (10 mL), and 0.1M diethyl ether·BF_3 (5 mL, 0.5 mmol) gave after 4 h, an oily residue that was purified on silica gel by flash chromatography (19:1, v/v, toluene–ethyl acetate). This material (0.47 g, 45%), a mixture of **31** and **34** was desilylated with tetrabutylammonium fluoride trihydrate (0.48 g, 1.52 mmol) in oxolane (10 mL), at first at 0° and then for 4 h at room temperature. The mixture was treated with water (100 mL) and extracted with dichloromethane (2 × 50 mL). The organic phase was dried, the solvent evaporated, and the oily residue purified by flash chromatography on silica gel (1:1, v/v, petroleum ether–ethyl acetate) to yield **32** (176 mg, 51%) and **35** (103 mg, 30%).

Compound **32**. Colorless oil, $[\alpha]_{578}^{23}$ +7.8° (*c* 1, chloroform), R_F (1:1, v/v, petroleum ether–ethyl acetate) 0.65; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 7.37–6.90 (m,

20 H, 4 C_6H_5), 6.57, 6.37 (2 d, 2 H, *J* 2.4 Hz, H-2,4), 5.63 (d, 1 H, $J_{1',2'}$ 2.4 Hz, H-1′), 5.03–4.06 (m, 10 H, 4 C_6H_5–CH_2OH), 4.24–3.68 (m, 6 H, 6 sugar H), 3.84 (s, 3 H, OMe), 3.64 (s, 3 H, OMe), and 3.77 (cm, 1 H, H-2′); ^{13}C-n.m.r. (22.6 MHz, $CDCl_3$): δ 160.2, 259.1 (C-3,5), 143.0 (C-1), 138.9, 138.5, 138.4 [C-1 (C_6H_5)], 128.2, 128.1, 127.9, 127.4, 127.2, 127.1 (C_6H_5), 114.6 (C-2), 103.4, 102.3 (C-4, C-6), 87.4, 79.9, 79.6, 75.7, 75.0, 74.3, 73.1, 72.6, 69.1 (4 C_6H_5–CH_2, 5 pyranose C), 65.2 (–CH_2OH), 56.1, and 55.8 (2 OCH_3).

Anal. Calc. for $C_{43}H_{46}O_8$ (690.8): C, 74.76; H, 6.71. Found: C, 74.42; H, 6.89.

Compound **35**. Colorless oil, $[\alpha]_{578}^{23}$ −2.5° (*c* 1, chloroform), R_F (1:1, v/v, petroleum ether–ethyl acetate) 0.38; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 7.37–6.86 (M, 20 H, 4 C_6H_5), 6.59, 6.62 (2 s, 2 H, H-2,6), 5.00 (d, 1 H, $J_{1',2}$ 10.1 Hz; H-1′), 4.97–4.05 (m, 8 H, 4 C_6H_5–CH_2), 4.41 (dd, 1 H, $J_{1',2'}$ 10.1, $J_{2',3'}$ 8.5 Hz, H-2′), 3.93–3.74 (m, 4 H, H-3′,4′,6′,6″), 3.80 (s, 3 H, OMe), 3.72 (s, 3 H, OMe), 3.57 (cm, 1 H, H-5′), and 1.80 (bs, 1 H, OH).

Anal. Calc. for $C_{43}H_{46}O_8$ (690.8): C, 74.76; H, 6.71. Found: C, 74.70; H, 6.64.

*3,5-Dimethoxy-2-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)benzyl acetate* (**33**). — As described for the preparation of compound **6**, **32** (0.13 g, 0.19 mmol) gave **33** (63 mg, 61%), colorless oil, $[\alpha]_{578}^{23}$ −10.5° (*c* 1, chloroform), R_F (2:3, v/v, petroleum ether–ethyl acetate) 0.62; ^{1}H-n.m.r. [400 MHz; ($^2H_6$)Me_2SO, 140°]: δ 6.53, 6.52 (2 s, 2 H, H-4,6), 5.47 (dd, 1 H, $J_{2',3'}$ 9.5, $J_{3',4'}$ 9.6 Hz, H-3′), 5.26 (d, 1 H, *J* 12.6 Hz, C*H*–OAc) 5.24 (dd, 1 H, $J_{1',2'}$ 9.9, $J_{2',3'}$ 9.5 Hz, H-2′), 5.16 (d, 1 H, *J* 12.6 Hz, C*H*–OAc), 5.02 (dd, 1 H, $J_{3',4'}$ 9.6, $J_{4',5'}$ 9.8 Hz, H-4′), 5.01 (d, 1 H, $J_{1',2'}$ 9.9 Hz, H-1′), 4.12 (cm, 2 H, H-6′,6″, 3.91 (cm, 1 H, H-5′), 3.80, 3.77 (2 s, 6 H, 2 OMe), 2.07, 1.99, 1.97, 1.91, and 1.68 (5 s, 15 H, 5 $COCH_3$).

Anal. Calc. for $C_{25}H_{32}O_{13}$ (540.5): C, 55.55; H, 5.97. Found: C, 55.29; H, 6.06.

*2,2-Dimethyl-7-methoxy-6-(2,3,4,6-tetra-*O*-benzyl-β-*D*-glucopyranosyl)-2*H*-chromen* (**36**). — As described for the preparation of **2**, procedure (*a*) applied to **1** (0.96 g, 1.40 mmol), 2,2-dimethyl-7-methoxy-2*H*-chromen (Precocene I: 0.29 g, 1.53 mmol) in anhydrous nitromethane (6 mL), and $ZnCl_2$ (0.35 g, 2.56 mmol) gave, after 1 h, an oily residue that was purified by flash chromatography on silica gel (19:1, v/v, toluene–ethyl acetate), yield 0.40 g (40%), colorless crystals, m.p. 107–108°; $[\alpha]_{578}^{23}$ +0.4° (*c* 1, chloroform); R_F (19:1, v/v, toluene–ethyl acetate) 0.43; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 7.33–6.91 (m, 20 H, 4 C_6H_5), 7.06 (s, 1 H, H-5), 6.38 (s, 1 H, H-8), 6.28 (d, 1 H, $J_{3,4}$ 9.8 Hz, H-4), 5.48 (d, 1 H, $J_{3,4}$ 9.8 Hz, H-3), 4.99–4.51 (m, 4 H, 2 C_6H_5–CH_2), 4.45 (dd, 1 H, $J_{1',2'}$ 10.3, $J_{2',3'}$ 10.3 Hz, H-2′), 4.01 (d, 1 H, $J_{1',2'}$ 10.3 Hz, H-1′), 3.81–3.60 (m, 9 H, 2 C_6H_5–CH_2, 5 sugar H), 3.72 (s, 3 H, OMe), 1.45, and 1.42 (2 s, 6 H, 2 Me).

Anal. Calc. for $C_{46}H_{48}O_7$ (712.9): C, 77.50; H, 6.79. Found: C, 77.54; H, 6.77.

*2,2-Dimethyl-7-methoxy-6-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)chro-*

man (**37**). — As described for the synthesis of compound **6, 36** (0.23 g, 0.32 mmol) gave **37** (0.13 g, 76%) after flash chromatography on silica gel (7:3, v/v, petroleum ether–ethyl acetate); colorless foam, $[\alpha]_{578}^{23}$ −18° (*c* 1, chloroform), R_F (same solvent system) 0.57; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 7.04 (s, 1 H, H-8), 6.29 (s, 1 H, H-5), 5.30–5.20 (m, 3 H, H-2′,3′,4′), 4.88 (d, 1 H, $J_{1',2'}$ 9.5 Hz, H-1′), 4.35–4.05 (m, 2 H, H-6′,6″), 3.90–3.75 (m, 1 H, H-5′), 3.76 (s, 3 H, OMe), 2.69 (cm, 2 H, H-4), 2.08, 2.05, 1.78 (4 s, 12 H, $COCH_3$), 1.77 (cm, 2 H, H-3), 1.34, and 1.29 (2 s, 6 H, 2 Me).

Anal. Calc. for $C_{26}H_{35}O_{11}$ (523.6): C, 59.65; H, 6.74. Found: C, 59.58; H, 6.79.

*1,3-Dimethoxy-4-(2,3,4,6-tetra-*O*-benzyl-β-*D*-glucopyranosyl)naphthalene* (**38**), *rotamers* **a** *and* **b**. — As described for the preparation of **2**, procedure (*a*) applied to **1** (1.19 g, 1.74 mmol), 1,3-dimethoxynaphthalene (0.35 mL, 1.86 mmol) in anhydrous dichloromethane (10 mL), and 0.56M diethylether · $ZnCl_2$ in dichloromethane (10 mL, 5.6 mmol) gave, after 30 min, an oily residue. This was purified by flash chromatography and elevated pressure chromatography on silica gel (4:1, v/v, petroleum ether–ethyl acetate) to yield **38a** (0.40 g, 32%) and **38b** (0.15 g 12%).

Rotamer **a**. $[\alpha]_{578}^{23}$ +27.0° (*c* 1, chloroform), R_F (4:1, v/v, petroleum ether–ethyl acetate) 0.38; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 8.71 (d, 1 H, $J_{7,8}$ 8.2 Hz, H-8), 8.17 (dd, 1 H, $J_{5,6}$ 8.2, $J_{5,7}$ 1.1 Hz, H-5), 7.40–6.98 (m, 22 H, 4 C_6H_5, H-6,7), 6.59 (s, 1 H, H-2), 6.04 (d, 1 H, $J_{1',2'}$ 3.7 Hz, H-1′), 4.99–4.35 (m, 6 H, 3 C_6H_5–CH_2), 4.13–4.06 (m, 3 H, C_6H_5–CH_2, H-3′), 4.01 (s, 3 H, OMe), 3.92 (cm, 1 H, H-2′), 3.78 (s, 3 H, OMe), and 3.81–3.74 (m, 4 H, H-4′,5′,6′,6″).

Rotamer **b**. $[\alpha]_{578}^{23}$ +27.6° (*c* 1, chloroform), R_F (4:1, v/v, petroleum ether–ethyl acetate) 0.33; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 8.53–8.49 (m, 1 H, H-8), 8.21–8.18 (m, 1 H, H-5), 7.35–7.05 (m, 22 H, 4 C_6H_5, H-6,7), 6.77–6.73 (m, 1 H, H-2), 5.43 (d, 1 H, $J_{1',2'}$ 9.9 Hz, H-1′), 4.99–4.48 (m, 6 H, 3 C_6H_5–CH_2), 4.27 (dd, 1 H, $J_{1',2'}$ 9.9, $J_{2',3'}$ 9.9 Hz, H-2′), 4.18–3.56 (m, 7 H, C_6H_5–CH_2, 5 sugar H), 4.03, and 3.89 (2 s, 6 H, 2 OMe).

Anal. Calc. for $C_{46}H_{46}O_7$ (710.9): C, 77.72; H, 6.92. Found (mixtures of rotamers): C, 77.48; H, 6.48.

*1,3-Dimethoxy-4-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)naphthalene* (**39**). — As described for the preparation of compound **6, 38** (rotamer **a**) (0.32 g, 0.42 mmol) gave **39** (0.15 g, 69%), after flash chromatography on silica gel (1:1, v/v, petroleum ether–ethyl acetate), colorless oil, R_F (4:1, v/v, petroleum ether–ethyl acetate) 0.43; ^{1}H-n.m.r. [250 MHz; ($^2H_6$–Me_2SO) 129°]: δ 8.30 (d, 1 H, $J_{7,8}$ 8.6 Hz, H-8), 8.08 (dd, 1 H, $J_{5,6}$ 8.2, $J_{5,7}$ 0.9 Hz, H-5), 7.55–7.44 (m, 1 H, H-7), 7.29 (dd, 1 H, $J_{5,6}$ 8.2, $J_{6,7}$ 8.9 Hz, H-6), 6.79 (s, 1 H, H-2), 5.67 (dd, 1 H, $J_{2',3'}$ 9.6, $J_{3',4'}$ 9.6 Hz, H-3′), 5.49 (d, 1 H, $J_{1',2'}$ 9.8 Hz, H-1′), 5.36 (dd, 1 H, $J_{3',4'}$ 9.6, $J_{4',5'}$ 9.6 Hz, H-4′), 5.21 (dd, 1 H, $J_{1',2'}$ 9.8, $J_{2',3'}$ 9.6 Hz, H-2′), 4.21–3.92 (m, 3 H, H-5′,6′,6″), 4.01, 3.95 (2 s, 6 H, 2 OMe), 2.03, 1.99, 1.91, and 1.55 (4 s, 12 H, 4 $COCH_3$).

Anal. Calc. for $C_{23}H_{30}O_{11}$ (482.5): C, 57.26; H, 6.27. Found: C, 57.49; H, 6.39.

10-(2,3,3,6-Tetra-O-benzyl-α,β-D-glucopyranosyl)anthrone (**40**). — (*a*) *Synthesis of 9-trimethylsilyloxyanthracene*. As described for the preparation of 3,5-dimethoxy-1-trimethylsilyloxybenzene from anthrone, 9-trimethylsilyloxyanthracene was obtained in 85% yield, b.p. 120° (1 MPa); ^{1}H-n.m.r. (80 MHz, $CDCl_3$): δ 8.56–8.13 (m, 5 H, H-1,4,5,8,10), 7.58 (m, 4 H, H-2,3,6,7), 0.35 (s, 9 H, $SiMe_3$); m.s.: *m/z* 266 (M^+) and 73 (100%).

(*b*) *Synthesis of* **40**. As described for the preparation of **2**, procedure (*a*) applied to **1** (0.79 g, 1.15 mmol), 9-trimethylsilyloxyanthracene (0.37 g, 1.38 mmol) in anhydrous dichloromethane (5 mL), and 0.25M diethyl ether·BF_3 in dichloromethane (4.20 mL, 1.1 mmol) gave, after 4 h, an oily residue that was purified by flash chromatography and elevated pressure chromatography on silica gel (4:1, v/v, petroleum ether–ethyl acetate); yield 0.33 g (40%) of a 1:1 mixture of the anomers which could not be separated; R_F (4:1, v/v, petroleum ether–ethyl acetate) 0.60; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 8.30 (m, 2 H, H-1,8), 7.90–7.20 (m, 26 H, aryl H), and 5.02–3.25 (m, 16 H, 4 CH_2, 7 sugar H, and H-10).

Anal. Calc. for $C_{48}H_{44}O_6$ (116.9): C, 80.42; H, 6.19. Found: C, 80.24; H, 6.31.

10-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)anthrone (**41**). — As described for the preparation of **2**, procedure (*a*) applied to compound **42**[19] (2.20 g, 4.50 mmol), 9-trimethylsilyloxyanthracene (1.40 g, 5.30 mmol) in anhydrous dichloromethane (10 mL), and $SnCl_4$ (0.52 mL, 2.74 mmol) gave, after 1 h, a solid residue that was purified by flash chromatography and elevated pressure chromatography on silica gel (3:2, v/v, petroleum ether–ethyl acetate); yield 0.79 g (34%), yellow powder, m.p. 137–138° (methanol–water), $[\alpha]_{578}^{23}$ −10.6° (*c* 1, chloroform); R_F (3:2, v/v, petroleum ether–ethyl acetate) 0.39; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 8.21 (m, 2 H, H-1,8), 7.64–7.34 (m, 6 H, H-2,7), 5.08 (dd, 1 H, $J_{2',3'}$ 9.2, $J_{3',4'}$ 9.7 Hz, H-3′), 4.73 (dd, 1 H, $J_{3',4'}$ 9.7, $J_{4',5'}$ 10.1 Hz, H-4′), 4.66 (dd, 1 H, $J_{1',2'}$ 10.1, $J_{2',3'}$ 9.2 Hz, H-2′), 4.41 (d, 1 H, *J* 1.5 Hz, H-10), 4.03–3.86 (m, 3 H, H-1′,6′,6″), 3.51–3.44 (m, 1 H, H-5′), 2.02, 1.96, 1.91, and 1.90 (4 s, 12 H, 4 $COCH_3$).

Anal. Calc. for $C_{28}H_{28}O_{20}$ (524.5): C, 64.12; H, 5.76. Found: C, 64.37; H, 5.84.

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A CONVENIENT SYNTHESIS OF *C*-α-D-RIBOFURANOSYL COMPOUNDS FROM 1-*O*-ACETYL-2,3,5-TRI-*O*-BENZYL-β-D-RIBOSE BY THE PROMOTION OF TRIPHENYLMETHYL PERCHLORATE

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ABSTRACT

In the presence of a catalytic amount of triphenylmethyl perchlorate (trityl perchlorate), 1-*O*-acetyl-2,3,5-tri-*O*-benzyl-β-D-ribose stereoselectively reacted with trimethylsilyl nucleophiles, such as trimethylsilyl enol ether, allylsilane, and trimethylsilyl cyanide, to give the corresponding *C*-α-D-ribofuranosyl derivatives in excellent yields. Similarly, a *C*-α-D-ribofuranosyl compound was obtained stereoselectively in high yield by use of a flow system with polymer-supported triphenylmethyl perchlorate, prepared from polystyrene-bound triphenylmethanol, packed in a glass-tube column.

INTRODUCTION

Stereoselective synthesis of functionalized *C*-glycosyl compounds is one of the most effective and used approaches to the preparation of *C*-nucleosides. Although several methods are already known for the synthesis of *C*-β-D-ribofuranosyl compounds[1], few general and versatile methods for the synthesis of *C*-α-D-ribofuranosyl compounds have been reported[2,3]. In a previous paper[4], we have shown that, in the presence of trityl perchlorate, 1-*O*-acyl sugars stereoselectively react with alcohols to afford the corresponding α-D-glycosides in good yields. We describe herein an equally efficient method for the preparation of *C*-α-D-ribofuranosyl compounds by the reaction of 1-*O*-acetyl-D-ribose with trimethylsilyl nucleophiles in the presence of a catalytic amount of trityl perchlorate[5]. We also report the convenient synthesis of *C*-α-D-ribofuranosyl compounds by simply passing the reagents through polymer-supported trityl perchlorate, packed in a glass-tube column.

RESULTS AND DISCUSSION

In the presence of a catalytic amount of trityl perchlorate (5 mol/100 mol), 1-*O*-acetyl-2,3,5-tri-*O*-benzyl-β-D-ribofuranose (**1**) reacted with the trimethylsilyl

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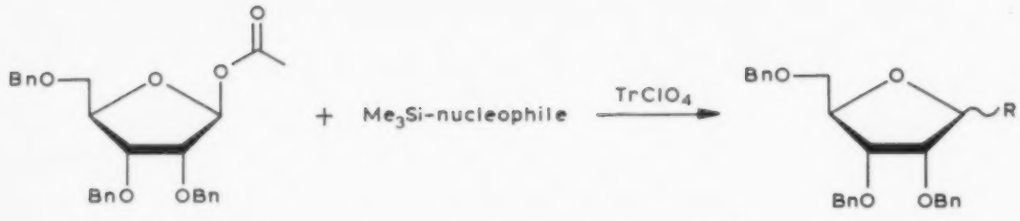


1

2 R = CH_2–CO–CMe_3
3 R = CH_2–CO–C_6H_5
4 R = $C_6H_9(O)O$
5 R = CH_2–CH=CH_2
6 R = CN

enol ether of *tert*-butyl methyl ketone to afford two anomers of 3,3-dimethyl-1-(2,3,5-tri-*O*-benzyl-D-ribofuranosyl)-2-butanone (**2**) (93%, 99:1 stereoselectivity). The ^{1}H-n.m.r. spectra showed two doublets of doublets for $-CH_2-$ protons at δ 3.00 and 2.95 for the major anomer (**2α**), and 2.70 and 2.55 for the minor anomer (**2β**). In the ^{13}C-n.m.r. spectra, C-2 resonated at δ 37.3 for the major anomer and 40.4 for the minor anomer (see Table I). Treament of the major anomer with sodium methoxide (under thermodynamic conditions) gave a mixture of **2α** and **2β** (**2α**:**2β** 21:29) which were separated by column chromatography on silica gel. The results suggested that **2α** and **2β** were the α-D and the β-D anomer, respectively, especially the definitive evidence[6] that the signal of the methylene group carbon atom in the α position to the carbonyl group of **2α** was at a field higher than that of the corresponding group of **2β***.

TABLE I

CHEMICAL SHIFTS (δ) OF THE METHYLENE OR METHINE GROUP CARBON ATOM IN POSITION α TO THE CARBONYL GROUP

Compound	*Chemical shifts of anomers*	
	α	β
2	37.3	40.4
3	39.2	42.7
4 (less polar)	51.0	53.4
(more polar)	52.0	53.3

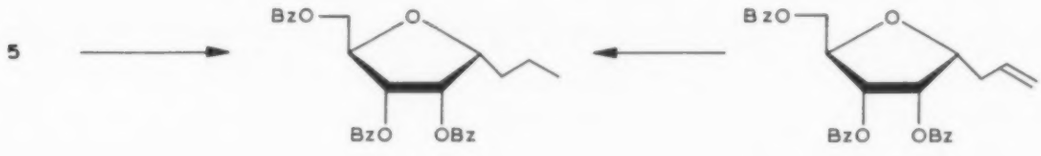
*In addition to the n.m.r. data, unambiguous chemical transformations of **2α** supported this assignment. Namely, the Bayer–Villiger oxidation of **2α**, followed by hydrolysis of the *tert*-butyl ester gave the corresponding carboxylic acid. Diazomethane treatment afforded the methyl ribofuranosylacetate whose spectral data were in complete agreement with those of the α-D anomer reported in the literature[6].

TABLE II

SYNTHESIS OF *C*-D-RIBOFURANOSYL COMPOUNDS **2–6**

Nucleophile	*Solvent*	*Product*	*Yield (%)*	*Ratio α to β*
Me_3–C(OSiMe_3)=CH_2	$(MeO)_2C_2H_4$	**2**	93	99:1
Ph–C(OSiMe_3)=CH_2	$(MeO)_2C_2H_4$	**3**	97	100:0
C_6H_9-OSiMe_3	$(MeO)_2C_2H_4$	**4**	93	96:4
Me_3Si-CH_2–CH=CH_2	$(MeO)_2C_2H_4$	**5**	90	100:0
Me_3SiCN	$(MeO)_2C_2H_4$	**6**	97	63:37
Me_3SiCN	Et_2O	**6**	93	93:7

Similarly, the α-D anomers **3α** and **4α** were stereoselectively obtained in excellent yields in the case of the silyl enol ethers derived from acetophenone and cyclohexanone. Also, the α-D anomer **5** was exclusively prepared by employing 4,4-dimethyl-4-sila-1-pentene as a *C*-nucleophile under the same reaction conditions (Table II). The structure of this compound was confirmed by debenzylation by hydrogenolysis, followed by benzoylation to afford the *O*-benzoyl-*C*-α-D-ribosyl compound **7** which was identical with a sample prepared by hydrogenation of the *C*-allyl-*O*-benzoyl-α-D-ribosyl compound **8**.

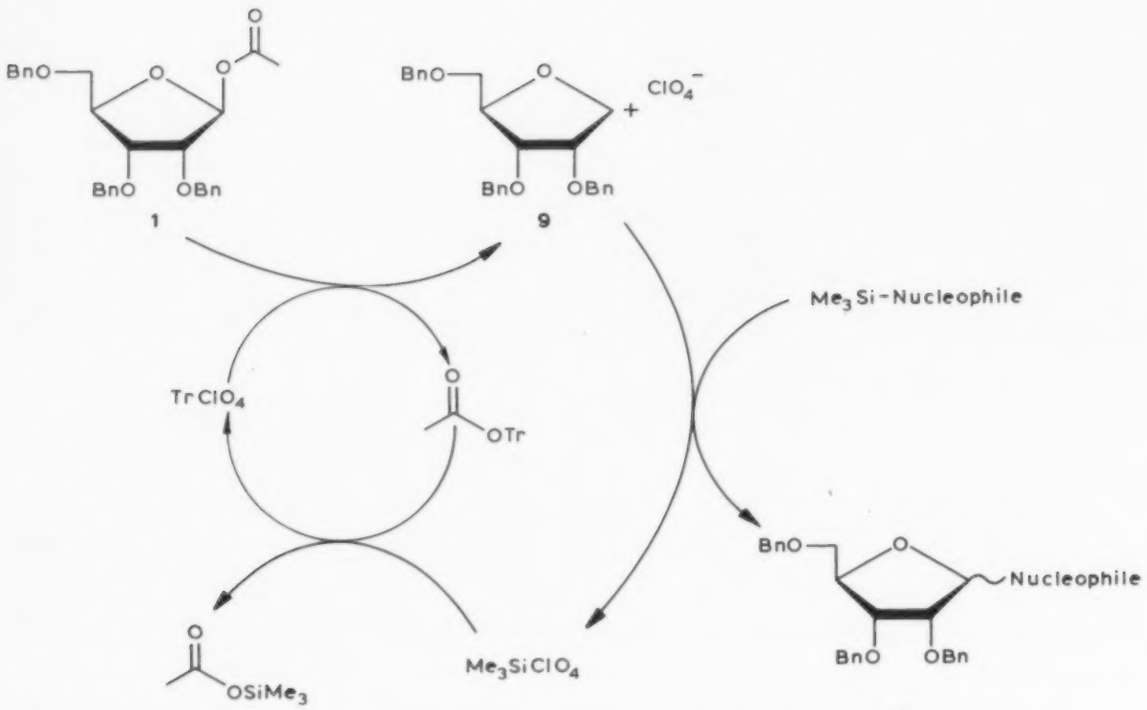


7 **8**

The reaction of **1** with trimethylsilyl cyanide under the same reaction conditions afforded an anomeric mixture, but the α-D anomer **6α** could be obtained stereoselectively by performing the reaction in ether solvent (Table II).

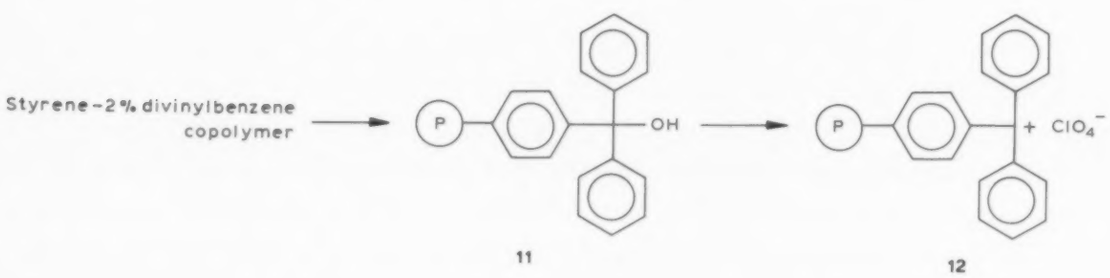
In the catalytic cycle (Scheme 1), trityl perchlorate activates **1** to generate the intermediate ion pair **9** and trityl acetate. This intermediate smoothly reacts with a trimethylsilylated nucleophile to give the *C*-ribofuranosyl compound **10** and trimethylsilyl perchlorate, which immediately reacts with trityl acetate to regenerate trityl perchlorate.

We have recently demonstrated the new possibilities of various trityl salts in synthetic reactions[3–5,7]. In these reactions, trityl salts effectively activate acyloxy groups of anomeric centers, alkoxy groups of acetals, aldehydes, or α,β-unsaturated ketones. The characteristic point of trityl salts, compared with other Lewis acids such as titanium tetrachloride, borontrifluoride, and tin tetrachloride, is that the reactions are effectively promoted by catalytic use. In order to develop a more efficient catalyst with wider applicability directed to synthetic control, the trityl



Scheme 1.

cation was immobilized on a polymer to prepare a polymer-bound trityl perchlorate[8], which was used for the synthesis of *C*-α-D-ribofuranosyl compounds. The polystyrene-bound triphenylmethanol **11** (ref. 9) was converted into the perchlorate salt **12** by treatment with perchloric acid in acetic anhydride; quantitative analysis[8] indicated that ~7% of the aromatic rings of polystyrene were converted into a perchlorate salt.



The *C*-glycosylation reaction was carried out in a flow system with the immobilized catalyst **12** packed in a glass-tube column. The dichloromethane solution of **1** and the trimethylsilyl enol ether of *tert*-butyl methyl ketone was charged onto the column and **2** was instantly obtained at the bottom (yield, 86%; ratio α to β, 24:1). Thus, *C*-α-D-ribofuranosyl compounds were successfully obtained in good yield by the flow-type reaction. This method has the practical advantage that the resulting compounds are separated quickly from the reaction system and that the catalyst is re-used.

EXPERIMENTAL

General. — Melting points were uncorrected. Optical rotations were measured with a Jasco DIP-181 digital polarimeter. ^{1}H-N.m.r. spectra for solutions in $CDCl_3$ were recorded with a Varian EM-390 spectrometer, and ^{13}C-n.m.r. spectra for solutions in $CDCl_3$ with a Jeol FX-90Q FT spectrometer. Column chromatography was performed on Silica gel 60 (Merck) or Wakogel C-200.

Trityl perchlorate was prepared by the method of Dauben *et al.*[10] and purified by that of Kochetkov *et al.*[11]. 1,2-Dimethoxyethane (DME) was distilled from $LiAlH_4$ before use. Polystyrene-bound trityl alcohol **11** was prepared according to a known method[9] from commercially available macroporous styrene–2% divinylbenzene copolymer (Mitsubishi Kasei Co.; DIAION HP-50).

*1-O-Acetyl-2,3,5-tri-O-benzyl-β-*D*-ribofuranose* (**1**). — To a solution of 2,3,5-tri-*O*-benzyl-D-ribofuranose (10 mmol) in pyridine (15 mL) was slowly added acetic anhydride (10 mL) at 0°. The mixture was stirred overnight at room temperature and was poured into a cold M HCl solution. The aqueous layer was extracted with ethyl acetate and the organic layer washed successively with aqueous $CuSO_4$, water, aqueous $NaHCO_3$, and water, dried, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give **1** (quant.), $[\alpha]_D^{26}$ +59° (*c* 1.0, chloroform); ^{1}H-n.m.r.: δ 1.90 (s, 3 H), 3.50–3.70 (m, 2 H), 3.75–4.05 (m, 2 H), 4.10–4.70 (m, 7 H), 6.10 (s, 1 H), and 6.70–7.70 (m, 15 H); ^{13}C-n.m.r.: δ 21.0, 98.9 (C-1), and 169.5.

Anal. Calc. for $C_{28}H_{30}O_6$: C, 72.71; H, 6.54. Found: C, 73.00; H, 6.73.

General procedure for the preparation of C-α-D-*ribofuranosyl compounds.* — Trityl perchlorate (15 μmol, 5 mg) was dried *in vacuo* for 1 h. To this was added the mixture of **1** (0.3 mmol, 139 mg) and a trimethylsilylated nucleophile (0.5 mmol) in 1,2-dimethoxyethane or ether (4 mL) at 0° under Ar. The mixture was stirred for 0.5–1 h at 0°. Phosphate buffer (pH 7) was added and the aqueous layer extracted with ether. The organic layer was dried, the solvent removed under reduced pressure, and the residue chromatographed on silica gel.

*3,3-Dimethyl-1-(2,3,5-tri-O-benzyl-α-*D*-ribofuranosyl)-2-butanone* (**2α**). — $[\alpha]_D^{25}$ +35° (*c* 1.0, chloroform); ^{1}H-n.m.r.: δ 1.05 (s, 9 H), 2.95 (dd, 1 H, *J* 5 Hz), 3.00 (dd, 1 H, *J* 8 Hz), 3.50 (m, 2 H), 3.95–4.85 (m, 10 H), and 7.00–7.40 (m, 15 H); ^{13}C-n.m.r.: δ 26.4, 37.3, 44.1, 70.2, 72.7, 73.4, 73.6, 76.5, 77.8, 79.1, 80.3, and 214.5

Anal. Calc. for $C_{32}H_{38}O_5$: C, 76.46; H, 7.62. Found: C, 76.35; H, 7.66.

*2-(2,3,5-Tri-O-benzyl-α-*D*-ribofuranosyl)acetophenone* (**3α**). — $[\alpha]_D^{24}$ +38° (*c* 1.1, chloroform); ^{1}H-n.m.r.: δ 3.25 (dd, 1 H, *J* 6, 17 Hz), 3.55 (dd, 1 H, *J* 5, 17 Hz), 3.45–3.65 (m, 2 H), 3.95–4.85 (m, 10 H), 6.95–7.55 (m, 18 H), and 7.80–8.00 (m, 2 H); ^{13}C-n.m.r.: δ 39.2, 70.3, 72.8, 73.5, 73.6, 76.7, 78.0, 79.6, 80.2, and 198.6.

Anal. Calc. for $C_{34}H_{34}O_5$: C, 78.14; H, 6.56. Found: C, 78.19; H, 6.43.

*2-(2,3,5-Tri-O-benzyl-α-*D*-ribofuranosyl)cyclohexanone* (**4α**). — Less polar isomer. M.p. 60.5–61.0°, $[\alpha]_D^{24}$ +57° (*c* 1.0, chloroform); ^{1}H-n.m.r.: δ 1.15–2.60

(m, 8 H), 2.70–3.10 (m, 1 H), 3.35–3.75 (m, 2 H), 3.95–4.90 (m, 10 H), and 7.10–7.40 (m, 15 H); ^{13}C-n.m.r.: δ 25.0, 28.6, 31.8, 42.6, 51.0, and 212.4

Anal. Calc. for $C_{32}H_{36}O_5$: C, 76.77; H, 7.25. Found: C, 76.76; H, 7.26.

More polar isomer. $[\alpha]_D^{25}$ +17° (*c* 1.1, chloroform); ^{1}H-n.m.r.: δ 1.30–2.45 (m, 8 H), 2.70–3.05 (m, 1 H), 3.50–3.70 (m, 2 H), 3.95–5.05 (m, 10 H), and 7.10–7.45 (m, 15 H); ^{13}C-n.m.r.: δ 24.4, 28.1, 30.0, 42.2, 52.0, and 211.3.

Anal. Calc. for $C_{32}H_{36}O_5$: C, 76.77; H, 7.25. Found: C, 76.06; H, 7.16.

Epimerization of **2α** *to give 3,3-dimethyl-1-(2,3,5-tri-*O*-benzyl-α-*D*-ribofuranosyl)-2-butanone* (**2β**). — The procedure of Ohrui *et al.*[6] was employed. Treatment of **2α** (0.3 mmol, 150 mg) with 0.1M sodium methoxide gave a mixture of **2α** (63 mg) and **2β** (87 mg) (yield, 84%; ratio α to β, 21:29).

2β. M.p. 30–31°, $[\alpha]_D^{25}$ +27° (*c* 1.0, chloroform); ^{1}H-n.m.r.: δ 1.05 (s, 9 H), 2.55 (dd, 1 H, *J* 5, 17 Hz), 2.70 (dd, 1 H, *J* 7, 17 Hz), 3.45–4.65 (m, 12 H), and 7.15–7.45 (m, 15 H); ^{13}C-n.m.r.: δ 26.1, 40.4, 44.2, 70.1, 71.6, 71.7, 73.4, 76.8, 77.6, 80.0, 80.8, and 213.3.

Anal. Calc. for $C_{32}H_{38}O_5$: C, 76.46; H, 7.62. Found: C, 76.44; H, 7.80.

Similarly, the β-D anomers **3β** and **4β** were obtained and the chemical shifts of the methylene or methine group carbon atom in position α to the carbonyl group are reported in Table I.

*3-(2,3,5-Tri-*O*-benzyl-α-*D*-ribofuranosyl)-1-propene* (**5**). — M.p. 55.5–56.0°, $[\alpha]_D^{24}$ +49° (*c* 1.0, chloroform); ^{1}H-n.m.r.: δ 2.35–2.65 (m, 2 H), 3.45–3.65 (m, 2 H), 3.90–4.30 (m, 4 H), 4.30–4.80 (m, 6 H), 4.80–5.20 (m, 2 H), 5.50–6.60 (m, 1 H), and 7.10–7.45 (m, 15 H); ^{13}C-n.m.r.: δ 34.3, 70.3, 72.7, 73.3, 73.4, 77.9, 79.6, 80.1, 80.3, 116.6, and 138.1.

Anal. Calc. for $C_{29}H_{32}O_4$: C, 78.35; H, 7.25. Found: C, 78.47; H, 7.28.

*1-(2,3,5-Tri-*O*-benzoyl-α-*D*-ribofuranosyl)propane* (**7**). — Debenzylation of **5** by hydrogenolysis in the presence of Pd–C, followed by benzoylation in the usual manner (benzoyl chloride–pyridine) afforded **7**, $[\alpha]_D^{23}$ +110° (*c* 0.47, chloroform); ^{1}H-n.m.r.: δ 0.95 (t, 3 H, *J* 6.6 Hz), 1.15–2.00 (m, 4 H), 4.30–4.80 (m, 4 H), 5.60–5.95 (m, 2 H), 7.15–7.70 (m, 9 H), and 7.70–8.15 (m, 6 H). The optical rotation and ^{1}H-n.m.r. data were consistent with those of an authentic sample prepared by hydrogenation (H_2; Pd–C) of 3-(2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl)-1-propene[3] (**8**).

Anal. Calc. for $C_{29}H_{28}O_7$: C, 71.30; H, 5.78. Found: C, 71.28; H, 5.67.

*2,3,5-Tri-*O*-benzyl-α-*D*-ribofuranosyl cyanide* (**7α**). — $[\alpha]_D^{24}$ +73° (*c* 1.0, chloroform); lit.[12] $[\alpha]_D^{25}$ +70° (*c* 1, chloroform); ^{1}H-n.m.r.: δ 3.25–3.45 (m, 2 H), 3.75–4.70 (m, 10 H), and 6.70–7.40 (m, 15 H); ^{13}C-n.m.r.: δ 68.6, 69.2, 72.6, 73.4, 73.5, 77.0, 77.9, 83.1, and 116.5.

Procedure for the preparation of C-*D*-*ribofuranosyl compounds by use of polymer-supported trityl perchlorate* (**12**) *packed in a glass-tube column*. — Polystyrene-bound triphenylmethanol (**11**; 60 mg) and chopped glass fiber (300 mg) was packed in a glass column (3 mm diam.). A solution of 70% $HClO_4$ (500 mg) in acetic anhydride (2 mL) was slowly passed through the column. The column was

washed successively with acetic anhydride (2 × 1 mL) and dichloromethane (2 × 1 mL), and dried *in vacuo*. The mixture of **1** (0.15 mmol) and a trimethylsilyl nucleophile (0.25 mmol) in dichloromethane (2 mL) was charged onto the column and the crude *C*-D-ribofuranosyl compound was obtained at the bottom. It was chromatographed on silica gel to afford the pure α-D compound.

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PALLADIUM(0)-ASSISTED SYNTHESIS OF *C*-GLYCOPYRANOSYL COMPOUNDS*

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ABSTRACT

Tetrakis(triphenylphosphine)palladium(0) effects the regio- and stereo-selective alkylation of 2-acetoxy-5,6-dihydro-2*H*-pyrans and 1-*S*-acetyl-1-thiohex-2-enopyranosides. Use of stabilized carbanions resulted in the formation of alkylated dihydropyrans with net retention at the oxygen-bearing carbon atom. Examples include the preparation of 2-[acetamidobis(ethoxycarbonyl)methyl]-5,6-dihydro-2*H*-pyran, 2-[acetamidobis(methoxycarbonyl)methyl]-6-ethoxy-5,6-dihydro-2*H*-pyran, and 2-[acetamidobis(methoxycarbonyl)methyl]-6-methoxymethyl-5,6-dihydro-2*H*-pyran. Use of nonstabilized carbanions, such as arylzinc chlorides, resulted in the formation of alkylated dihydropyrans and *C*-glycosyl compounds with net inversion at the oxygen-bearing carbon atom. Examples include the preparation of 2-[(6-ethoxy-5,6-dihydro-2*H*-pyranyl)methyl]-4,4-dimethyl-2-oxazoline, *trans*-methoxymethyl-2-phenyl-5,6-dihydro-2*H*-pyran, *trans*-methoxymethyl-2-vinyl-5,6-dihydro-2*H*-pyran, *trans*-2-[2,2-bis(ethoxy)ethyl]-6-methoxymethyl-5,6-dihydro-2*H*-pyran, (4,6-di-*O*-methyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)benzene, (2,3-dideoxy-4,6-di-*O*-methyl-β-D-*erythro*-hex-2-enopyranosyl)benzene, 1-(2,3-dideoxy-4,6-di-*O*-methyl-α- and -β-D-*erythro*-hex-2-enopyranosyl)naphthalene, 4-(2,3-dideoxy-4,6-di-*O*-methyl-α- and -β-D-*erythro*-hex-2-enopyranosyl)toluene, and 1-(2,3,6-trideoxy-4-*O*-methyl-α-L-*erythro*-hex-2-enopyranosyl)naphthalene.

INTRODUCTION

C-Glycopyranosyl-containing natural products have been the focus of increasing synthetic interest. Due to the varying complexity of the synthetic targets, methods have been developed which can be categorized by the method used to construct the *C*-glycosyl unit[2]. Some groups have utilized stereocontrolled procedures to construct the pyranoside ring with the requisite carbon bond to C-1 of the eventual pyranosyl residue intact, prior to ring formation. These include the

*Palladium-assisted Reactions, part III. For part II, see ref. 1.
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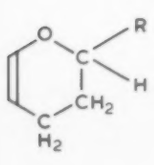
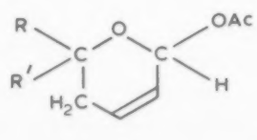
elegant hetero Diels–Alder condensation[3–5], and ring closure methods following Wittig condensations[6] or asymmetric epoxidation[7]. In contrast, the readily available chiral pool of pyranosides has made it increasingly attractive to construct the carbon–carbon bond directly to C-1 of an intact pyranosyl residue. Current examples include the enolate Claisen rearrangement applications[8], glycosyllithium additions[9–13], glycosyl-radical trapping with alkenes[14], nucleophilic displacements on glycal methanesulfonates[15], several variations of Lewis acid or metal-mediated generation of the oxocarbenium ions, followed by nucleophilic addition[16–26], allylstannane coupling with glycosyl halides[27], and organometallic methods utilizing iron[28], manganese[29], and palladium(II) addition–elimination methods[30–32].

As part of our interest in the development of palladium-controlled functionalization of carbohydrates[33], we reasoned that a nucleophilic palladium(0) reagent-controlled, *C*-glycosylation method would offer additional versatility and generality in complementing these above-mentioned methods, whose stereoselectivity depends largely on control by the carbohydrate substrate. A reagent-controlled α or β selective *C*-glycosylation using tetrakis(triphenylphosphine)-palladium(0) [$Pd(PPh_3)_4$] was predicted to be highly stereoselective, based on the elegant work of Trost[34,35] demonstrating that stabilized carbanions react with inversion on carboxylic π-allyl complexes, while Matsushita and Negishi[36] showed that organozinc halides react with carbocyclic π-allylpalladium complexes with retention. Our preliminary studies verified that the same stereoselectivity could be realized in the alkylation of substituted acetoxydihydropyrans, and furthermore the alkylation was completely regioselective, occurring exclusively at the ring oxygen-bearing carbon atom[1].

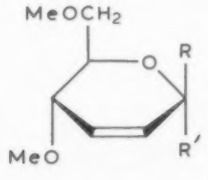
Herein we describe additional details of the alkylation of dihydropyrans and the successful extension of these results to the synthesis of substituted (hex-2-enopyranosyl)arenes. These compounds were chosen as model compounds representing more complex synthetic targets which would be converted to *C*-glycosyl analogs of 11-deoxydaunomycinone and possibly aklavinone[37]. Such a method would allow preparation of these analogs by direct attachment of an intact aglycon nucleophile to a rhamnal-derived palladium complex, as compared to the procedure recently reported by Acton *et al.*[38] in which the D ring was constructed



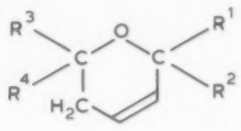
1 R = H
2 R = OEt
3 R = CH_2OMe



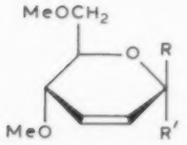
4 R = R′ = H
5 R = OEt, R′ = H
6 R = H, R′ = OEt
7 R = CH_2OMe, R′ = H
8 R = H, R′ = CH_2OMe



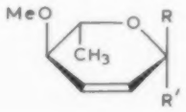
9 R = OAc, R′ = H
10 R = H, R′ = OAc
11 R = SAc, R′ = H



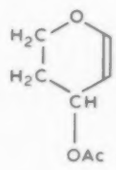
12 $R^1 = C(NHAc)(CO_2Et)_2$, $R^2 = R^3 = R^4 = H$
13 $R^1 = C(NHAc)(CO_2Me)_2$, $R^2 = R^4 = H, R^3 = OEt$
14 $R^1 = R^4 = H, R^2 = C(NHAc)(CO_2Me)_2$, $R^3 = OEt$
15 $R^1 = C(NHAc)(CO_2Me)_2$, $R^2 = R^4 = H, R^3 = CH_2OMe$
16 $R^1 = R^4 = H, R^2 = C(NHAc)(CO_2Me)_2$, $R^3 = CH_2OMe$
17 $R^1 = R^4 = H, R^2 = Ph, R^3 = OEt$
18 $R^1 = Ph, R^2 = R^4 = H, R^3 = OEt$
19 $R^1 = R^4 = H, R^2 =$ (4,4-dimethyl-2-oxazolin-2-yl)methyl, $R^3 = OEt$
20 $R^1 =$ (4,4-dimethyl-2-oxazolin-2-yl)methyl, $R^2 = R^4 = H, R^3 = OEt$
21 $R^1 = R^4 = H, R^2 = Ph, R^3 = CH_2OMe$
22 $R^1 = R^4 = H, R^2 = CH=CH_2, R^3 = CH_2OMe$
23 $R^1 = R^4 = H, R^2 = CH_2CH(OEt)_2, R^3 = CH_2OMe$
24 $R^1 = CH_2CH(OEt)_2, R^2 = R^4 = H, R^3 = CH_2OMe$



25 R = H, R′ = Ph
26 R = Ph, R′ = H
27 R = H, R′ = 1-naphthyl
28 R = 1-naphthyl, R′ = H
29 R = H, R′ = *p*-tolyl
30 R = *p*-tolyl, R′ = H



31 R = H, R′ = SAc
32 R = 1-naphthyl, R′ = H



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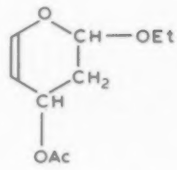

34

by use of a Diels–Alder reaction of an ABC ring dienophile with a daunosamine-containing 2,4-pentadiene. Such *C*-glycosyl analogs are resistant to metabolic deactivation by reductive deglycosylation, and, as a result, possibly will have an increased therapeutic potential[39,40].

RESULTS AND DISCUSSION

Initial experiments to effect palladium(0)-catalyzed *C*-glycosylation were attempted on acetylated carbohydrate glycals. Attempts to alkylate the readily avaiable 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol or 3,4-di-*O*-acetyl-1,5-anhydro-2,6-dideoxy-L-*arabino*-hex-1-enitol in either oxolane or *N,N*-dimethylformamide in the presence of tetrakis(triphenylphosphine)palladium(0)

$[Pd(PPh_3)_4]$ and triphenylphosphine (PPh_3), according to methodology developed by Trost[34], were unsuccessful, with nearly quantitative recovery of the starting glycal. This failure to undergo allylic alkylation was not surprising in view of the lack of examples of alkylation of enolether allylic acetates in which the oxygen atom is attached at the terminus of the allylic double bond. To our knowledge, such allylic acetates do not undergo nucleophilic attack by palladium because they are too electron rich. This result was also consistent with the observation of Trost and Keinan[41] who found a poor yield and, also, that significantly longer reaction times were required to alkylate a 2-ethoxyallylic acetate. Our attention then turned to the alkylation of electron-deficient allylic acetates. Owing to the lack of readily available 1-*O*-acetylhex-2-enopyranoses, initial experiments were carried out on acetoxydihydropyrans in order to define the scope and stereochemical results of the *C*-glycosylation. The dihydropyranyl acetates **4–6** were prepared by a modification of the method of Hurd and Edwards[42] using lead tetraacetate. It was found that the yield of the desired 2-acetoxy-5,6-dihydropyran (**4**) could be increased relative to that of 4-acetoxy-5,6-dihydro-4*H*-pyran when the reaction was carried out at −5–0° in benzene with lead tetraacetate free of residual acetic acid. Thus, the reaction of each dihydropyran **1–3** afforded the corresponding 2-acetoxydihydropyrans **4–6** in the range of 45–50%. When the reaction was performed at −5–0°, the product was usually contaminated with only up to 20% of its allylic isomer. The preponderant stereoisomers formed under these reaction conditions were the *cis* acetoxylated products **5** and **7** with the overall *cis* stereoselectivity greatest for acetoxylation of the methoxymethyldihydropyran **3**. The steric structures were determined by comparison of the ^1H- and ^{13}C-n.m.r. spectra of the *cis* and *trans* isomers. In all cases, the less shielded C-2 and C-6 signals of the ^{13}C-n.m.r. spectrum were assigned to the *cis* isomer in accordance with the expected *γ-gauche* effect previously observed in cyclohexanes and also in *C*-glycopyranosyl compounds[43]. The pertinent spectral data used to identify each stereoisomer are shown in Table I.

When the lead tetraacetate acetoxylation procedure of Hurd and Edwards[42] was attempted on 3-deoxyglycals, only skeletal rearrangement products were

TABLE I

STEREOCHEMICAL ASSIGNMENTS OF DIHYDROPYRANYLACETATES

Reactant	*Products (ratio)*	*N.m.r. data*[a]			
		Cpd.	*δ ^{13}C-2*	*δ ^{13}C-6*	*δ H-2, multiplicity, $J_{2,3}$ (Hz)*
1	**4**	**4**	87.90	57.27	6.24–6.09 m
2	**5, 6** (3:1)	**5**	89.89	94.72	6.401, ddd, 0.8
		6	86.34	94.12	6.34–6.32, m 9 (whh)
3	**7, 8** (>20:1)	**7**	89.01	67.98	6.423, ddd, 1.6

[a]For a solution in $CDCl_3$.

isolated. Consequently, the desired 1-*O*-acetylhex-2-enopyranoses **9** and **10** were prepared by a procedure described by Fraser-Reid *et al.*[44]. Thus, either ethyl 2,3-dideoxy-4,6-di-*O*-methyl-α-D-*erythro*-hex-2-enopyranoside or 1,5-anhydro-2-deoxy-3,4,6-tri-*O*-methyl-D-*arabino*-hex-1-enitol were treated with acetic anhydride and boron trifluoride etherate in benzene to afford the 1-*O*-acetyl-2,3-dideoxy-4,6-di-*O*-methyl-D-*erythro*-hex-2-enopyranoses **9** and **10** in a 1:1 ratio. Chromatographic separation of these anomers was not possible without accompanying allylic isomerization. Variation in the reaction temperature and time did not improve the stereoselectivity in favor of either anomer. Consequently, we have developed a method to prepare stereo- and regio-selectively 1-*S*-acetyl-2,3-dideoxy-1-thio-β-D-*erythro*-hex-2-enopyranoses which serve as adequate synthetic equivalents to 1-*O*-acetylhex-2-enopyranoses. They can also be prepared in a more stereo- and regioselective fashion and seem to be stable to silica gel chromatography and amenable to anomer separation[45].

The palladium(0)-catalyzed *C*-glycosylation of dihydropyranyl acetates **4–8** was carried out with a variety of stabilized and nonstabilized carbanions. Several adducts were prepared and the results are summarized in Table II. With a stabilized carbanion and the acetoxydihydropyran in *N,N*-dimethylformamide, the use of 10 moles percent of $Pd(PPh_3)_4$ and 1 mole percent of triphenylphosphine at 60–70° for 12 h led to the formation of the alkylated dihydropyran with net retention of configuration. The yields of isolated products, after chromatography on silica gel, were in the range of 65–98%, based on the allylic acetate. When dihydropyranyl acetate **7** was stirred with *N,N*-dimethylformamide in the presence of 10 moles percent of $Pd(PPh_3)_4$ for 2 h prior to the addition of triphenylphosphine or carbanion, the major project isolated with dimethyl sodio(acetamido)malonate was the *trans* isomer **16**, the product of net inversion. This result suggested that the intermediate

TABLE II

Pd(0)-CATALYZED ALKYLATION OF DIHYDROPYRANYL ACETATES

Reactants	*Carbanion*	*Method*[a]	*Products (ratio)*	*Yield (%)*[b]
4	$NaC(NHAc)(CO_2Et)_2$	*A*	**12**	80
5 + **6** (3:1)	$NaC(NHAc)(CO_2Me)_2$	*A*	**13, 14** (3:1)	85
7	$NaC(NHAC)(CO_2Me)_2$	*A*	**15**	90
7	$NaC(NHAc)(CO_2Me)_2$	[c]	**16**	88
5 + **6** (3:1)	PhZnCl	*B*	**17** + **18** (3:1)	98
5 + **6** (3:1)	$Me_2C_3H_2NOCH_2ZnCl$	*B*	**19** + **20** (3:1)	42
7	PhZnCl	*B*	**21**	94
7	$CH_2{=}CHZnCl$	*B*	**22**	97
5 + **6** (3:1)	$CH(OEt)_2CH_2ZnCl$	*B*	**23** + **24** (3:1)	79

[a]Method *A*: (a) $Pd(PPh_3)_4$ (0.1 equiv.), PPh_3 (1 equiv.), *N,N*-dimethylformamide, room temperature, 20 min; (b) carbanion, 70°, 18 h. Method *B*: (a) $Pd(PPh_3)_4$ (0.05 equiv.), oxolane, room temperature, 15 min; (b) RZnCl oxolane, room temperature, 6 h. [b]Yield based on acetate, after chromatography. [c]See text.

TABLE III

STEREOCHEMICAL ASSIGNMENTS OF ALKYLATED DIHYDROPYRANS BY N.M.R. SPECTROSCOPY[a]

Compd.	$\delta^{13}C$		$\delta^{1}H$-2	$J_{1,2}$ (Hz)
	C-2	*C-6*		
12	76.81	64.16	4.935–4.914	1.7
13	77.74	98.61	5.059	1.6
14	71.14	95.60	5.030	1.9
15	77.73	69.40	5.105	1.56
16	69.66	69.42	5.084	2.4[b]
17	70.43	95.79	5.220	0.8
19	65.37	95.25	4.56–4.52	[c]
20	71.38	98.32	4.58–4.54	[c]
21	73.99	66.54	5.30	1.83
22	73.19	66.80	4.69	2.16
23	65.08	66.47	4.99	1.5
24	69.43	70.73	[c]	[c]

[a]For solutions in $CDCl_3$. [b]At 318 K. [c]Could not be determined.

palladium–dihydropyranyl complex had isomerized prior to alkylation, a result which had previously been observed for carbocyclic π-allylpalladium complexes. In further experiments, it was verified that the *cis, trans* equilibration of dihydropyranyl acetate **7** only occurred in *N,N*-dimethylformamide, and did not occur in oxolane. There is a possibility that the mechanism of the alkylation in these two solvents is different, but at present no experiments have been performed that verify this postulate. This isomerization in *N,N*-dimethylformamide is an example of reagent-controlled stereoselectivity, and enables the preparation of either stereoisomer from the same starting dihydropyranyl acetate **7**.

The structures of each of the alkylated dihydropyrans were confirmed by n.m.r. spectrometry, primarily on the basis of ^{1}H-chemical shifts and coupling constants associated with H-2 and the gamma-*gauche* effect on C-2 and C-6 in each of the adducts. Comparative spectral data for the various adducts are summarized in Table III. Each *cis* adduct exists primarily in a single conformation, whereas the *trans* adducts equilibrate between their two half-chair forms and show some temperature dependence in their n.m.r. spectra.

When nonstabilized carbanions were used, such as phenylzinc chloride or allylzinc chloride, the products formed resulted from net inversion, which is consistent with transmetallation of the organozinc reagent to palladium, followed by reductive elimination with retention of configuration. Again, the structure of each of these adducts was verified by spectral comparisons with those of previously described compounds, and a good correlation was obtained for the chemical shifts and coupling constants, even in the absence of any minor isomers. These palladium-assisted alkylations of dihydropyranyl acetates are completely regio- and stereo-

TABLE IV

Pd(0)-CATALYZED *C*-GLYCOSYLATION WITH ARYLZINC CHLORIDES

Reactants (ratio)	*ArZnCl*	*Products (ratio)*	*Yield (%)*[a]
9 + **10** (1:1)	Phenyl	**25** + **26** (1:1)	30
11 + α (86:14)	1-Naphthyl	**27** + **28** (86:14)	16
11 + α (93:7)	*p*-Tolyl	**29** + **30** (94:6)	21
11 + α (72:28)	*p*-Tolyl	**29** + **30** (75:25)	21
31	1-Naphthyl	**32**	23

[a]Based on carbohydrate reactant.

selective, and the stereoselectivity thus far observed has been found to be identical with that for alkylations of carboxylic allylic acetates.

These stereo- and regio-selective alkylation reactions were extended to the preparation of aryl-substituted hex-2-enopyranosides. Thus either 1-*O*- or 1-*S*-acetylhex-2-enopyranosides could be converted into their corresponding *C*-glycosyl arenes by treatment with their respective arylzinc chloride in the presence of $Pd(PPh_3)_4$ in oxolane for 5–6 h at room temperature, affording a moderate yield of their respective (hex-2-enopyranosyl)arenes. These reactions were completely stereoselective, each 1-*S*-acetyl-1-thio-β-D-hex-2-enopyranose being converted into the corresponding α-D-glycosylarene with net inversion of configuration at C-1. The reaction was also completely regioselective in favor of alkylation exclusively at C-1. Although the present yields are only moderate (20–30%) based on thioacetate, they represent the yield after both column and liquid chromatographic separation, and the reaction seems reproducible on both a small and medium scale. We are currently in the process of optimizing the yield with respect to both the catalyst and the ratio of nucleophile to thioacetate. The quality of the palladium catalyst in this reaction was especially crucial to its reproducibility. The results for each of these reactions are summarized in Table IV, and the relevant spectroscopic data on

TABLE V

STEREOCHEMICAL ASSIGNMENTS OF GLYCOSYLARENES

Compd.	*N.m.r. data*[a]				
	^{1}H δ H-1 ($J_{1,2}$)	*^{13}C δ C-1*	*^{13}C δ C-5*	*$^1J_{C\text{-}1,H\text{-}1}$*	*$[\alpha]_D^{25}$*[b] *(degrees)*
25	5.28 (2.0)	74.06	70.21	145	+19
26	5.16 (1.6)	77.49	72.21	[c]	[c]
27	5.92 ([d])	71.75	70.35	144	+61
29	5.23–5.30 ([d])	74.08	69.89	[c]	+37
32	5.91–5.97 ([d])	77.99	67.36	134	−64

[a]For solutions in (^{2}H)chloroform. *J* values in hertz. [b]For solutions in chloroform. [c]Value unavailable. [d]Broad singlets, whh ~5–10 Hz varying with temperature.

which the stereochemical assignments are based are shown in Table V. In the absence of any crystalline products from this reaction to date, we have based our stereochemical assignments on comparative data including ^{1}H- and ^{13}C-n.m.r. spectrometry and specific rotation. The chemical shifts and coupling constants for H-1 are in accord with each product assigned as the α-D anomer. The $^{1}J_{C\text{-}1,H}$ data are included in Table V primarily to indicate that the close proximity of the values strongly supports the assignment of the same stereoisomer from each reaction. These coupling-constant values are reasonable for α anomers when compared to other data for substituted pyranosides, considering the differences in the electronegativity of various substituents and the possible effects of the double bond on the dihedral angle between the O–H bond and the oxygen atom lone-pairs[46]. The specific rotation for each α-D anomer agrees with the rotation reported for a comparable α-D-glycosylbenzene prepared by Czernecki and Dechavenne[31]. Our data are consistent with the observation that each *C*-α-D-glycosyl compound exists as a mixture of equilibrating $^{O}H_{5}$ and $^{5}H_{O}$ conformers. The observed gamma-*gauche* effect for the phenyl anomers was also useful in helping to assign the steric structure of other α-D-glycosylarenes when only one isomer was formed in the reaction. Thus, we have demonstrated that nucleophilic substituents can be directly attached to C-1 of carbohydrates by a method in which the stereo- and regio-chemical outcome of the reaction is controlled by both the reactant and the substrate.

EXPERIMENTAL

General methods. — Optical rotations were measured with a Rudolph Autopol III polarimeter. I.r. spectra were recorded with a Perkin–Elmer 281 or a Nicolet F.t.i.r. spectrometer. N.m.r. spectra were recorded for solutions in (^{2}H)chloroform with either Varian XL-100, Varian XL-200, Nicolet-200, or Bruker WM-500 spectrometers; ^{1}H-n.m.r. spectra are reported referenced to the signal of internal tetramethylsilane at 100, 200, or 500 MHz; ^{13}C-n.m.r. spectra were recorded at 25.2, 50.3, or 125.7 MHz and are referenced to the signal of (^{2}H)chloroform (δ 77.00); multiplicities from off-resonance decoupling experiments are in agreement with the assignments, and ^{1}J values were obtained in the gated mode. Mass spectra were obtained with either a Hewlett–Packard 5985 low-resolution or a Kratos MS-80 medium-resolution mass spectrometer in either the low-resolution electron impact (e.i.) or chemical ionization (c.i., methane) mode, or in the high-resolution mode with peak matching to perfluorokerosene. T.l.c. and column chromatography were performed on Silica gel GF_{254} (230–400 mesh, Merck). Analytical l.c. (7 MPa) was performed in a 30-cm Waters 5-μ Microporasil column and semipreparative l.c. with a 50-cm Whatman Magnum 9 silica column. Conventional processing signified the drying of organic solutions (Na_2SO_4), filtration, and concentration under diminished pressure. All solvents were distilled shortly before use from an appropriate drying agent. Ether, oxolane, and benzene were distilled from sodium metal in the presence of diphenylketyl anion. $ZnCl_2$ was

dried by flaming *in vacuo* (1 mm). All air-sensitive reactions were performed under an atmosphere of Ar. Tetrakis(triphenylphosphine)palladium(0) was purchased from Aldrich or prepared according to the procedure of Coulson[47].

*2-Acetoxy-5,6-dihydro-2*H*-pyran* (**4**) *and 4-acetoxy-5,6-dihydro-4*H*-pyran* (**33**). — A modification of the procedure of Hurd and Edwards[42] was used to prepare **4**. Lead tetraacetate (Aldrich) was dried *in vacuo* to a fine (white to beige) powder and stored under strictly anhydrous conditions. To a mechanically stirred solution of 3,4-dihydro-2*H*-pyran (**1**; 9.22 g, 0.11 mol) in dry benzene (110 mL), at −5° under N_2, was added anhydrous lead tetraacetate (44 g, 0.99 mol) in small portions over 1 h during which the reaction temperature was kept at or ~0° with an ice–salt bath. About 15 min after the final portion of lead tetraacetate had been added, the mixture was allowed to warm temperature with stirring continued for an additional 15 min. The mixture was filtered through a bed of Filter Aid and the filter pad rinsed with dry benzene. The combined benzene filtrates were evaporated *in vacuo* to give crude **4** which was purified by vacuum distillation (1.2 Pa) to give a ~9:1 mixture of **4** and **33** (7.04 g, 45%); b.p. 37° (1.2 Pa); $\nu_{max}^{CHCl_3}$ 2990, 2980 (CH), 1750 (C=O), 1360, 1260, and 1070 cm^{-1} (C–O); ^{1}H-n.m.r. (**4**; 100 MHz): δ 6.24–6.09 (m, *J* 10 Hz, H-2,3), 5.82–5.65 (m, *J* 10 Hz, H-4), 3.98–3.86 (m, *J* 10.4 Hz, H-6,6′), 2.65–1.86 (m, H-5,5′), and 2.14 (s, $OCOCH_3$); ^{13}C-n.m.r. (**4**; 25.2 MHz): δ 168.52 (C=O), 129.33 (C-3), 122.98 (C-4), 87.90 (C-2), 57.27 (C-6), 24.78 (C-5), and 21.88 ($COCH_3$); m.s. (e.i.; 200°): *m/z* 142.1 (3.2%; M^+) and 82.1 (39%; M − HOAc); ^{13}C-n.m.r. [**33**; 25.2 MHz, $(CD_3)_2SO$]: δ 169.58 (C=O), 147.88 (C-2), 99.38 (C-3), 61.89, 61.59 (C-4,6), 27.98 (C-5), and 20.86 ($COCH_3$).

*2-Acetoxy-6-ethoxy-5,6-dihydro-2*H*-pyrans* (**5** *and* **6**) *and 4-acetoxy-2-ethoxy-3,4-dihydro-2*H*-pyran* (**34**). — Following the procedure for the preparation of **4**, 2-ethoxy-3,4-dihydro-2*H*-pyran (Aldrich; 47.8 g, 373 mmol) was treated with lead tetraacetate (149 g, 336 mmol) at 0°, followed by vacuum distillation (0.8 Pa) of the crude product to give >20:1 ratio of **5** plus **6** and **34** (32.0 g, 46%, **5**:**6** ~3:1); b.p. 54–58° (0.8 Pa); ν_{max}^{film} 3045 (C=CH), 2980, 2960, 2900 (CH), 1740 (C=O), 1340, 1290, and 1120 cm^{-1} (C–O); ^{1}H-n.m.r. (**5**; 500 MHz): δ 6.401 (ddd, *J* 3.8, 1.6, and 0.8 Hz, H-2); 5.981 (dddd, *J* 10.0, 5.2, 2.8, 1.2 Hz, H-4), 5.714 (dddd, *J* 10.0, 2.8, 2.7, 1.6 Hz, H-3), 4.961 (ddd, *J* 7.8, 3.8, 0.6 Hz, H-6), 3.917 (ddd, *J* 9.6, 7.1, 7.1, 7.1 Hz, OCH), 3.538 (dddd, *J* 9.6, 7.1, 7.1, 7.1 Hz, OCH), ~2.3 (m, H-5b), 2.242 (dddd, *J* 7.8, 2.8, 2.7, 1.5 Hz, H-5a), 2.074 (s, $OCOCH_3$), $J_{2,3}$ 1.6, $J_{2,6}$ 3.8, $J_{2,4}$ 0.8 or 1.2, $J_{3,4}$ 10, $J_{3,4a}$ 2.7 or 2.8, $J_{4,5a}$ 5.2, $J_{4,5b}$ 2.7 or 2.8, and $J_{5a,6}$ 7.8 Hz; ^{13}C-n.m.r. (**5**; 25.2 MHz): δ 168.16 (C–O), 127.19 (C-3), 122.83 (C-4), 94.72 (C-6), 89.89 (C-2), 64.21 (OCH_2), 30.78 (C-5), 21.82 ($COCH_3$), and 15.77 (CH_3); ^{1}H-n.m.r. (**6**; 500 MHz): δ 6.34–6.32 (m, whh 9 Hz, H-2); 6.06–6.02 (m, H-4), 5.77–5.74 (m, H-3), 5.03–5.01 (m, H-6), 3.83–3.77 (m, OCH), 3.52–3.47 (m, OCH), 2.47–2.41 (m, H-5,5′), and 2.029 (s, $OCOCH_3$); ^{13}C-n.m.r. (**6**; 25.2 MHz): δ 168.56 (C=O), 125.34 (C-3), 121.90 (C-4), 94.12 (C-6), 86.34 (C-2), 63.24 (OCH_2), 29.71 (C-5), 21.82 ($COCH_3$), and 15.77 (CH_3); m.s. (c.i., CH_4, 100°; mixture): *m/z* 187 (5%, MH^+) and 127 (100%), MH^+ − HOAc).

When the reaction was performed in toluene at −40° (with warming to 0° before filtration), none of the allylic isomer **34** was detected by ^{1}H-n.m.r. The *cis*-to-*trans* ratio was unaltered and the yield of distilled compound was 42%; b.p. 53° (0.1 Pa).

cis-(**7**) *and* trans-*2-Acetoxy-6-methoxymethyl-5,6-dihydro-2*H-*pyran* (**8**). — According to the procedure for the preparation of **4**, **3** (15.3 g, 120 mmol) was treated with lead tetraacetate (47.6 g, 107 mmol) at 0°, followed by vacuum distillation (2.4 Pa) of the crude product to give a ~6:1 ratio of **7** and **8** (10.1 g, 46%); b.p. 64–67° (1.0 Pa); ν_{max}^{film} 3010 (C=CH), 2930, 2900 (CH), 1740 (C=O), 1245, 1200, and 1140 cm^{-1} (C–O); ^{1}H-n.m.r. (**7**; 500 MHz): δ 6.243 (ddd, *J* 3.2, 1.6, 1.6 Hz, H-2), 6.079 (dddd, *J* 10.0, 6.0, 1.6, 1.6 Hz, H-3), 5.711 (dddd, *J* 10.0, 3.1, 2.9, 1.4 Hz, H-4), 4.044 (dddd, *J* 11.3, 5.5, 3.6, 3.6 Hz, H-6), 3.430 (ddd, *J* 16.4, 11.3, 6.0 Hz, CH_2), 3.338 (s, OCH_3), 2.144 (ddddd, *J* 17.9, 11.3, 2.8, 1.9, 1.9 Hz, H-5b), 2.028 (s, $OCOCH_3$), 1.963 (dddd, *J* 17.9, 5.9, 3.5, 1.4 Hz, H-5a); irradiation at δ 6.243 caused H-3 to collapse to a ddd minus, $J_{2,3}$ 1.6 Hz, H-4 to collapse to a ddd minus, $J_{2,4}$ 3.1 Hz, and H-5b to collapse to a ddd minus $J_{2,5}$ 1.9 Hz, and no change at H-5a; thus, for **7**: $J_{2,3}$ 1.6, $J_{2,4}$ 3.1, $J_{2,5a}$ 1.9, $J_{2,5a}$ 0, $J_{3,4}$ 10.0, $J_{3,5a}$ 6.0, $J_{3,5b}$ 1.6 or 1.9, $J_{4,5a}$ 1.4, $J_{4,5b}$ 2.8 or 2.9, $J_{5a,5b}$ 17.9, $J_{5b,6}$ 11.3, $J_{5a,6}$ 3.5 or 3.6, $J_{6,7a}$, $J_{6,7b}$ 3.6, 5.5 or 6.0, and $J_{7a,7b}$ 16.4 Hz; ^{13}C-n.m.r. (**7**; 25.2 MHz): δ 168.27 (C=O), 128.54 (C-2), 122.73 (C-4), 89.01 (C-2), 74.43 (C-7), 67.98 (C-6), 59.32 (OCH_3), 26.86 (C-5), and 21.87 ($COCH_3$); ^{1}H-n.m.r. (**8**; 500 MHz): δ 6.542 (d, *J* 6.1 Hz, H-2), 5.090 (ddd, *J* 5.8, 3.6, and 2.1 Hz, H-3), 4.936 (ddd, *J* 5.8, 5.8, 1.7 Hz, H-4), 4.06 (m, H-6), 3.504 (m, OCH_2), 3.373 (s, OCH_3), 2.017 (s, $OCOCH_3$), and ~1.83 (m, H-5,5′); ^{13}C-n.m.r. (**8**; 25.2 MHz): δ 169.04 (C=O), 147.19 (C-2), 98.70 (C-3), 74.44 (C-7), 70.70 (C-6), 62.95 (C-4), 59.46 (OCH_3), 30.98 (C-5), and 21.92 ($COCH_3$); m.s. (c.i., CH_4, 100°; mixture): *m/z* 187 (6%, MH^+) and 127 (100%, MH^+ − HOAc).

Anal. (h.r.e.i.m.s.) Calc. for $C_7H_{11}O_2$ (M^+ − OAc): 127.0759. Found: 127.0759.

*1-*O*-Acetyl-2,3-dideoxy-4,6-di-*O*-methyl-α-* (**9**) *and* -β-D-erythro-*hex-2-eno-pyranose* (**10**). — The procedure described is an adaptation of that described by Fraser-Reid *et al.*[44]. 1,5-Anhydro-2-deoxy-3,4,6-tri-*O*-methyl-D-*arabino*-hex-1-enitol (1 g, 5.3 mmol) was dissolved in a solution of acetic anhydride (6.71 g, 65.7 mmol) in dry benzene (13.8 mL, 0.4M) with stirring at room temperature. BF_3·diethyl ether complex (16 mg, 0.1 mmol, commercial grade) was then added and the mixture stirred for 6 h. It was then poured into ice-cold 0.63M $NaHCO_3$ (50 mL) with vigorous stirring for 30 min. The mixture was transferred to a separatory funnel and extracted with ether (3 × 50 mL). The combined ether extracts were washed with water (1 × 50 mL), dried (Na_2SO_4), and evaporated *in vacuo*. Methanol was evaporated from the residue several times to remove traces of acetic acid from the crude product (630 mg, 57%); t.l.c. (30%, v/v, ethyl acetate–hexane) indicated the presence of two main products (R_F 0.55 and 0.45) with a minor decomposition product (R_F 0.11); ^{1}H-n.m.r. (100 MHz): δ 6.51 (d), 6.28 (br. s),

6.25 (br. s), 6.14 (br. s), 6.05–6.01 (m), 5.88–5.44 (m), 4.96 (br. s), 4.90 (br. s), 3.89–3.83 (m), 3.75–3.48 (m), 3.46 (s, OCH_3), 3.44 (s, OCH_3), 3.42 (s, OCH_3), 2.26 (s, OAc), 2.12 (s, OAc), and 2.11 (s, OAc). A repetition of this procedure starting from ethyl 2,3-dideoxy-4,6-di-*O*-methyl-α-D-*erythro*-hex-2-enopyranoside (1 g, 5 mmol) produced a similar mixture of products (650 mg, 60%). The mixture was used directly without purification for the synthesis of **25** and **26**.

General procedure for Pd(0)-catalyzed C-glycosylation. — This is a modification of the procedure developed by Trost and coworkers for allylic alkylation[48]. A dihydropyranyl acetate (1 equiv.) was dissolved in an appropriate solvent (dry oxolane or *N,N*-dimethylformamide, Ar saturated, 0.15M total volume). With stabilized carbanions (Method *A*), triphenylphosphine (1 equiv.) and $Pd(PPh_3)_4$ (0.1 equiv.) were then added with stirring under Ar. Carbanions (1.05 equiv.) were prepared and added, within 5 min, either as solids or in solution. The mixture was heated to 60–70° over a 12–18 h period, and then cooled to room temperature, partitioned between equal volumes of water and ether, and the aqueous layer extracted with additional ether (3 times). The combined extracts were washed with saturated NaCl solution (water when *N,N*-dimethylformamide was used), dried (Na_2SO_4), and evaporated *in vacuo*. Chromatography of the crude residue on silica gel afforded the corresponding *C*-glycosyl compounds in good yields (65–90% based on the dihydropyranyl acetate). With nonstabilized carbanions (Method *B*) only oxolane was used. $Pd(PPh_3)_4$ (0.25–0.50 equiv.), without added PPh_3, was then added, followed immediately by a preformed (0°) solution of carbanion in oxolane. The mixture was stirred for 3–6 h at room temperature and then worked up as described in Method *A* (yield, 85–98%, based on the dihydropyranyl acetate).

*2-[Acetamidobis(ethoxycarbonyl)methyl]-5,6-dihydro-2*H*-pyran* (**12**). — 2-Acetoxy-5,6-dihydro-2*H*-pyran (**4**; 200 mg, 1.41 mmol) and diethyl sodioacetamidomalonate (345 mg, 1.44 mmol) in *N,N*-dimethylformamide (20 mL) were treated according to Method *A* to afford **12** as a pale-yellow oil after chromatography (270 mg, 80%); R_F (30%, v/v, EtOAc–hexane) 0.5; $\nu_{max}^{CHCl_3}$ 3420 (NH), 3015 (C=CH), 2980, 2920, 2860 (CH), 1755, 1740 (C=O ester), 1680 (C=O amide), 1655 (C=C), 1280 and 1085 cm^{-1} (C–O); ^{1}H-n.m.r. (500 MHz): δ 6.076–6.043 (dddd, *J* 10.5, 4.1, 1.6, 1.6 Hz, H-3), 5.899–5.856 (dddd, *J* 10.5, 4.3, 2.3, 1.2 Hz, H-4), 4.935–4.914 (dddd, *J* 4.8, 1.7, 1.7, 1.7 Hz, H-2), 4.303–4.113 (m, 4 H, CO_2CH_2), 3.922–3.882 (m, H-6*e*), 3.617–3.567 (m, H-6*a*), 2.244–2.099 (m, H-5*e*), 1.972 (s, $OCOCH_3$), 1.857–1.795 (m, H-5*a*), 1.23 (t, *J* 7.0 Hz, CH_3), and 1.202 (t, *J* 7.0 Hz, CH_3); ^{13}C-n.m.r. (25.2 MHz): δ 168.8 (NC=O), 167.00 (C=O), 165.41 (C=O), 126.45 (C-3), 126.21 (C-4), 76.81 (C-2), 68.62 (C-1′), 64.16 (C-5), 62.76, 61.94 (OCH_2), 24.82 (C-5), 23.13 ($OCOCH_3$), and 14.02 (CH_3).

*2-[Acetamidobis(methoxycarbonyl)methyl]-6-ethoxy-5,6-dihydro-2*H*-pyrans* (**13** *and* **14**). — Compounds **5** and **6** (574 mg, 3.08 mmol) in *N,N*-dimethylformamide (20 mL) were treated with dimethyl sodio(acetamido)malonate (720 mg, 3.4 mmol) according to Method *A* to afford a yellow oil (660 mg, 85% based on **5** and **6** of 80% purity), **13** and **14** in the ratio 3:1, which were partially separated

by chromatography. Mixture of **13** and **14**: R_F 0.36 (**5**), 0.28 (**6**) (40%, v/v, ethyl acetate–petroleum ether); $\nu_{max}^{CHCl_3}$ 3420 (NH), 3040 (C=CH), 2980, 2950, 2910, 2870 (CH), 1740, 1670 (C=O), 1620 (C=C), 1270–1180, 1115, 1040, 1020, and 980 cm^{-1} (C–O); ^{1}H-n.m.r. (**13**; 500 MHz): δ 6.673 (br. s, 1 H, NH), 6.019 (dddd, *J* 10.4, 2.1, 1.9, 1.6 Hz, H-5), 5.763–5.722 (m, H-4), 5.059 (ddd, *J* 7.0, 3.6, 1.6 Hz, H-2), 4.646 (dd, *J* 6.4, 5.2 Hz, H-6), 3.790 (s, CO_2CH_3), 3.725 (s, CO_2CH_3), 3.75–3.70 (m, 1 H, OCH), 2.146–1.906 (m, H-3,3′), 1.976 (s, $COCH_3$), and 1.172 (t, *J* 7.1 Hz, CH_3); ^{13}C-n.m.r. (**13**, 25.2 MHz): δ 124.87 (C-5), 124.48 (C-6), 98.61 (C-2), 77.74 (C-6), 64.50 (OCH_2), 53.80 (CO_2CH_3), 27.31 (CO_2CH_3), 42 (C-2), 23.72 ($NHCOCH_3$), and 16.11 (OCH_2CH_3); the C=O and C-1′ signals could not be assigned; ^{1}H-n.m.r. (**14**; 500 MHz): δ 6.557 (br. s, 1 H, NH), 6.094 (dddd, *J* 10.4, 1.9, 1.0, 1.0 Hz, H-5), 5.756 (dddd, *J* 10.4, 4.6, 2.4 Hz, H-4), 5.030 (ddd, whh 8 Hz, *J* 4.6, 3.7, 1.9 Hz, H-2), 4.636 (dd, *J* 6.4, 5.2 Hz, H-6), 3.806 (s, CO_2CH_3), 3.746 (s, CO_2CH_3), 3.667 (q, 1 H, *J* 9.6, 7.1 Hz, OCH), 3.431 (q, *J* 9.6, 7.1 Hz, OCH), 2.006 (s, $COCH_3$), and 1.202 (t, *J* 7.1 Hz, CH_3); ^{13}C-n.m.r. (**14**; 25.2 MHz): δ 167.65 (C=O), 166.00 (C=O), 164.45 (C=O), 123.76 (C-5), 122.40 (C-4), 95.60 (C-2), 71.14 (C-6), 68.24 (C-1), 62.96 (OCH_2), 53.66 (CO_2CH_3), 53.13 (CO_2CH_3), 30.12 (C-3), 23.62 ($COCH_3$), and 15.87 (OCH_2CH_3); an upfield shift in the signals corresponding to the *cis* isomer of approximately 0.15 p.p.m. was observed in the fraction from which this ^{13}C-n.m.r. spectrum was recorded; m.s. (c.i., CH_4, 100°): *m/z* 316 (44%, MH^+), 344 (12%, $MC_2H_5^+$), 356 (9%, $MC_3H_5^+$), and 270 (100%, MH − EtOH).

Anal. (h.r.c.i.m.s.) Calc. for $C_{12}H_{16}NO_6$: 270.0977. Found: 270.0978.

cis-*2*-[*Acetamidobis(methoxycarbonyl)methyl*]-*6-methoxymethyl-5,6-dihydro-2H-pyran* (**15**). — Compound **7** (560 mg, 3 mmol) in *N,N*-dimethylformamide (20 mL) was treated with dimethyl sodio(acetamido)malonate (700 mg, 3.3 mmol) according to Method *A* to afford **15** as a pale-yellow oil after chromatography (680 mg, 90%, based on **7** of 80% purity), R_F (30%, v/v, ethyl acetate–petroleum ether) 0.15; $\nu_{max}^{CHCl_3}$ 3400 (NH), 3030 (C=CH), 1740, 1680 (C=O), 1645 (C=C), 1280, 1220, 1120, and 1060 cm^{-1} (C–O); ^{1}H-n.m.r. (500 MHz): δ 6.626 (br. s, NH), 6.056 (dddd, *J* 10.5, 2.6, 2.6, 1.6 Hz, H-3), 5.909 (dddd, *J* 10.5, 5.0, 3.0, 2.0 Hz, H-4), 5.105 (ddd, *J* 4.8, 2.6, 2.0 Hz, H-2), 3.960 (dddd, *J* 8.0, 5.7, 4.8, 4.3 Hz, H-6), 3.811 (s, CO_2CH_3), 3.714 (s, CO_2CH_3), 3.370 (dd, *J* 10.1, 5.7 Hz, $CHOCH_3$), 3.332 (s, 3 H, OCH_3), 3.313 (dd, *J* 10.1, 4.8 Hz, $CHOCH_3$), 2.05–1.92 (m, H-5,5′), and 1.987 (s, $COCH_3$); ^{13}C-n.m.r. (25.2 MHz): δ 167.45 ($NCOCH_3$), 165.95, 164.94 (CO_2CH_3), 124.38 (C-3), 123.86 (C-4), 77.73 (C-2, tentative), 74.53 (CH_2OCH_3), 69.55 [$CNHAc(CO_2CH_3)_2$], 69.40 (C-6), 53.85, 53.03 (CO_2CH_3), 59.37 (OCH_3), 26.77 (C-5), and 23.67 ($NHCOCH_3$); m.s. (c.i., CH_4, 100°): *m/z* 316 (98%, MH^+) and 190 [39%, $MH^+ - C(CO_2Me)_2NHAc$].

Anal. (h.r.c.i.m.s.) Calc. for $C_{14}H_{22}NO_7$: 316.1390. Found: 316.1399.

trans-*2*-[*Acetamidobis(methoxycarbonyl)methyl*]-*6*-*methoxymethyl*-*5,6*-*dihydro*-*2H*-*pyran* (**16**). — Compound **7** (500 mg, 2.7 mmol) was stirred with $Pd(PPh_3)_4$ (310 mg, 0.37 mmol) in *N,N*-dimethylformamide (20 mL) for 2 h, and

then dimethyl sodio(acetamido)malonate (580 mg, 2.74 mmol) and PPh_3 (704 mg, 2.7 mmol) were added according to Method *A*. Chromatography afforded **16** as a yellow oil (599 mg, 88% based on **7** of 80% purity) which was shown by ^{1}H-n.m.r. spectroscopy to be an equilibrium mixture of conformers which coalesced at 318 K, R_F (30%, v/v, ethyl acetate–petroleum ether) 0.15; $\nu_{max}^{CHCl_3}$ 3400 (NH), 3030 (C=CH), 2980, 2950, 2880 (CH), 1740, 1680 (C=O), 1645 (C=C), 1280, 1220, 1120, and 1060 cm^{-1} (C–O); ^{1}H-n.m.r. (500 MHz, 298 K): δ 6.784 (br. s, NH), 6.022–5.983 (m, H-3), 5.877–5.831 (m, H-4), 5.603–5.040 (m, H-2), 3.943–3.893 (m, H-6), 3.759, 3.755 (2 s, CO_2CH_3), 3.662, 3.657 (2 s, CO_2CH_3), 3.338–3.296 (m, OCH_2), 3.283, 3.728 (2 s, OCH_3), 2.0–1.8 (m, 2 H, C-5,5′), 1.941, and 1.937 (2 s, $COCH_3$); ^{1}H-n.m.r. (500 MHz, 318 K): δ 6.708 (br. s, 1 H, NH), 6.058 (dddd, *J* 10.5, 4.1, 2.3, 1.7 Hz, H-3), 5.889 (dddd, *J* 10.5, 5.1, 2.7, 2.5 Hz, H-4), 5.084 (ddd, *J* 4.6, 2.5, 2.4 Hz, H-2), 3.951 (m, H-6), 3.795 (s, CO_2CH_3), 3.705 (s, CO_2CH_3), 3.39–3.30 (m, OCH_2), 3.325 (s, 3 H, OCH_3), 2.06–1.86 (m, H-5,5′), and 1.979 (s, $COCH_3$); ^{13}C-n.m.r. (50.2 MHz, 298 K): δ 169.00 ($NCOCH_3$), 167.47, 166.40 (CO_2CH_3), 125.22 (C-3), 124.64 (C-4), 74.49 (CH_2OCH_3), 69.66 (C-2), 69.42 [$CNHCOCH_3(CO_2CH_3)_2$], 59.20 (OCH_3), 53.67, 52.82 (CO_2CH_3), 26.08 (C-5), and 22.95 ($COCH_3$); m.s. (c.i., CH_4, 100°): *m/z* 316 (4.5%, MH^+) and 127 [100%, $MH^+ - C(CO_2Me)_2NHAc$].

*6-Ethoxy-2-phenyl-5,6-dihydro-2*H*-pyrans* (**17** *and* **18**). — Compounds **5** and **6** (280 mg, 1.5 mmol; ratio **5** to **6**, 3:1) in oxolane (10 mL) were treated with phenylzinc chloride [prepared by adding M phenylmagnesium bromide in oxolane (1.6 mL) to anhydrous $ZnCl_2$ (210 mg, 1.55 mmol) in oxolane (3.4 mL)] at 0° according to Method *B*. Chromatography on silica gel afforded **17** and **18** as a pale-yellow oil (245 mg, 98% based on **5** and **6** of 80% purity; ratio **17** to **18**, 3:1); R_F (20%, v/v, ethyl acetate–petroleum ether) 0.94; $\nu_{max}^{CHCL_3}$ 3070, 3030 (C=CH), 2980, 2920 (CH), 1590 (C=C), 1130, 1050, and 1025 cm^{-1} (C–O); ^{1}H-n.m.r. (**17**; 500 MHz): δ 5.84–5.83 (m, H-3,4), 5.220 (ddd, *J* 3.5, 3.5, 0.8 Hz, H-6), 5.056 (ddd, *J* 4.6, 0.8, 0.8 Hz, H-2), 3.911 (dddd, *J* 9.8, 7.1, 7.1, 7.1 Hz, $OCHCH_3$), 3.559 (dddd, *J* 9.8, 7.1, 7.1, 7.1 Hz, $OCHCH_3$), 2.564–2.509 (m, 1 H, H-5*e*), 2.184–2.132 (m, 1 H, H-5*a*), and 1.271 (dd, *J* 7.1, 7.1 Hz, CH_3); ^{13}C-n.m.r. (**17**; 125.6 MHz): δ 140.98, 128.65, 128.43, 127.77 (C-3), 127.33, 121.75 (C-4), 95.79 (C-6), 70.43 (C-2), 63.12 (OCH_2), 29.98 (C-5), and 15.21 (CH_3); ^{13}C-n.m.r. (**18**; 125.7 MHz, tentative): δ 128.66 (C-2), 125.55 (C-4), 95.88 (C-6), 30.76 (C-5), and 15.32 (CH_3).

*2-[6-Ethoxy-5,6-dihydro-2*H*-pyranyl)methyl]-4,4-dimethyl-2-oxazolines* (**19** *and* **20**). — Compounds **5** and **6** (1.383 g, 7.4 mmol) in oxolane (35 mL) were treated with 5,5-dimethyl-2-oxazolinozinc chloride (1.2 g, 8.2 mmol) in oxolane according to Method *B*. Chromatography on silica gel afforded **19** and **20** in two major fractions as an orange oil (600 mg, 42% based on **5** and **6** of 80% purity). The first fraction was substantially enriched in **20**, and the latter in **19**, as determined by the ^{1}H-n.m.r. spectra. The two fractions were combined and a ^{13}C-n.m.r. spectrum was recorded, which allowed a determination of the *cis, trans* ratio; ratio **19** to **20**, 3:1; R_F (30%, v/v, ethyl acetate–petroleum ether) 0.4 (**20**) and 0.3 (**19**);

ν_{max}^{film} 3020 (C=CH), 2970, 2930, 2900 (CH), 1670 (C=N), and 1060 cm^{-1} (C–O); ^{1}H-n.m.r. (**20**; 500 MHz): δ 5.726–5.648 (m, H-3′,4′), 4.681 (dd, *J* 6.3, 4.9 Hz, H-6′), 4.57–4.54 (m, H-2), 3.9808 (ddddd, *J* 9.6, 7.1, 7.1, 7.1 Hz, OCH), 3.878 (s, OCH_2), 3.494 (dddd, *J* 9.6, 7.1, 7.1, 7.1 Hz, OCH), 2.610 (dd, *J* 14.9, 7.0 Hz, CH–C-2), 2.423 (dd, *J* 14.9, 7.6 Hz, CH–C-2), 2.42–1.99 (m, 2 H, H-5′a,5′b), 1.237 (s, 6 H, CH_3), and 1.196 (dd, *J* 7.1, 7.1 Hz, CH_3); ^{13}C-n.m.r. (**20**; 125.7 MHz): δ 162.79 (C-2), 128.17 (C-3′), 123.52 (C-4′), 98.32 (C-6′), 78.76 (C-5), 71.38 (C-2′), 66.93 (C-4), 62.77 (OCH_2), 34.19 (C–C-2), 30.87 (C-3), 28.22 (CH_3), and 15.01 (OCH_2CH_3); m.s. (c.i., CH_4, 100°): *m/z* 240 (75%, MH^+), 268 (14%, $MC_2H_5^+$), 280 (7%, $MC_3H_5^+$), 194.1 (100%, MH^+ − EtOH) and 166 (4%, MH^+ − EtOH − C≡O).

Anal. (h.r.c.i.m.s.) Calc. $C_{13}H_{22}NO_3$: 240.1600. Found: 240.1600.

^{1}H-n.m.r. (**19**; 500 MHz): δ 5.726–5.648 (m, H-3′,4′), 4.955 (dd, *J* 4.6, 1.7 Hz, H-5′), 4.56–4.52 (m, H-2′), 3.802 (dddd, *J* 9.8, 7.1, 7.1, 7.1 Hz, OCH), 3.89 (s, OCH_2), 3.500 (dddd, *J* 9.8, 7.1, 7.1, 7.1 Hz, OCH), 2.536 (dd, 1 H, *J* 14.2, 8.1 Hz, CH–C-2), 2.433 (dd, *J* 14.2, 6.1 Hz, CH–C-2), 2.42–1.99 (m, 2 H, H-5′), 1.240 (s, CH_3), 1.234 (s, CH_3), and 1.193 (dd, *J* 7.1, 7.1 Hz, CH_3); ^{13}C-n.m.r. (**19**; 125.7 MHz): δ 162.98 (C-2), 127.42 (C-3′), 122.26 (C-4′), 95.25 (C-6′), 78.89 (C-5), 66.93 (C-4), 65.37 (C-6), 63.85 (OCH_2), 33.82 (C–C-2), 29.82 (C-3), 28.22 (CH_3), and 15.0 (OCH_2CH_3).

trans-*6-Methoxymethyl-2-phenyl-5,6-dihydro-2*H-*pyran* (**21**). — Compound **7** (280 mg, 1.5 mmol) in oxolane (10 mL) was treated with phenylzinc chloride [prepared by adding phenylmagnesium bromide (1.6 mL, 1.6 mmol) to anhydrous $ZnCl_2$ chloride (211 mg, 1.55 mmol) in oxolane (5 mL) at 0°] according to Method *B*. Chromatography afforded **21** as a yellow oil (230 mg, 94% based on **7** of 80% purity), R_F (20%, v/v, ethyl acetate–petroleum ether) 0.8; ν_{max}^{film} 3030, 3020 (C=CH), 2990, 2930, 2890, 2820 (CH), 1600 (C=C), 1120, and 1090 cm^{-1} (C–O); ^{1}H-n.m.r. (500 MHz): δ 7.43–7.25 (m, 5 H, Ph), 6.042 (dddd, *J* 10.3, 4.7, 1.8, 1.8 Hz, H-3), 6.008 (dddd, *J* 10.3, 3.0, 1.3, 1.3 Hz, H-4), 5.301 (m, whh 6 Hz, H-2), 3.77 (dddd, *J* 9.9, 5.7, 4.0, 3.9 Hz, H-6), 3.439 (dd, *J* 10.2, 5.7 Hz, $CHOCH_3$), 3.380 (dd, *J* 10.2, 4.1 Hz, $CHOCH_3$), 3.323 (s, OCH_3), 2.244–2.177 (m, H-5b), and 2.008–1.953 (m, H-5a), irradiation at δ 5.301 caused $J_{2,3}$ 1.8 Hz to disappear from δ 6.042, $J_{2,4}$ 3.0 Hz to disappear from δ 6.008, and δ 2.210 to collapse into a dddd pattern (*J* 17.3, 10.0, 1.8, 1.3 Hz); $J_{3,4}$ 10.3, $J_{2,4}$ 3.0, $J_{2,3}$ 1.8, $J_{5b,6}$ 10.0, $J_{5a,6}$ 3.9, $J_{3,5b}$ 4.7, $J_{3,5a}$ 1.8, and $J_{4,5a} = J_{4,5b}$ 1.3 Hz; ^{13}C-n.m.r. (50.2 MHz): δ 140.87 (C-3), 128.24, 127.86, 127.53, 127.45, 125.26 (C-4), 75.16 (CH_2OCH_3), 73.99 (C-2), 66.54 (C-6), 59.16 (OCH_3), and 27.04 (C-5).

Anal. (h.r.c.i.m.s.) Calc. for $C_{13}H_{17}O_2$: 205.1229. Found: 205.1222.

trans-*6-Methoxymethyl-2-vinyl-5,6-dihydro-2*H-*pyran* (**22**). — Compound **7** (280 mg, 1.5 mmol) in oxolane (10 mL) was treated with vinylzinc chloride [prepared by the addition of vinylmagnesium bromide (1.55 mL, 1.55 mmol) to anhydrous $ZnCl_2$ (211 mg, 1.55 mmol) in oxolane (5 mL) at 0°] according to Method *B*. Chromatography afforded **22** as a yellow oil (180 mg, 97% based on **7** of

80% purity), R_F (20%, v/v, ethyl acetate–petroleum ether) 0.9; $\nu_{max}^{CHCl_3}$ 3060, 3010 (C=CH), 2980, 2930, 2880 (CH), 1650, 1620 (C=C), 1220, 1130, 1100, 1050 (C–O), 980, and 910 cm^{-1} (–CH=CH_2); ^{1}H-n.m.r. (500 MHz): δ 5.905 (ddd, *J* 17.2, 10.5, 5.0 Hz, H-X), 5.867 (dddd, *J* 10.2, 5.6, 2.2, 2.1 Hz, H-3), 5.711 (dddd, *J* 10.2, 3.5, 2.6, 1.5 Hz, H-4), 5.211 (ddd, *J* 9.6, 1.6, 1.6 Hz, H-B), 5.183 (ddd, *J* 3.6, 1.5, 1.5 Hz, H-A), 4.688 (dddddd, whh 9 Hz, *J* 5.0, 3.5, 2.6, 2.1, 1.6, 1.5 Hz, H-2, measured indirectly from decoupling H-2), 3.848 (dddd, *J* 10.2, 6.3, 3.7, 3.4 Hz, H-6), 3.437 (dd, 1 H, *J* 10.2, 6.3 Hz, $CHOCH_3$), 3.381 (dd, *J* 10.2, 3.7 Hz, $CHOCH_3$), 3.357 (s, OCH_3), 2.062 (ddddd, *J* 17.3, 10.3, 2.6, 2.5, 2.5 Hz, H-5b), 1.876 (ddddd, *J* 17.3, 5.5, 2.3, 2.3, 1.2 Hz, H-5a); irradiation at 2344.6 Hz (δ 4.688) caused loss of *J* 5.0 Hz from δ 5.905, of *J* 2.1 Hz from δ 5.867, of *J* 3.5 Hz from δ 5.711, of *J* 1.6 Hz from δ 5.211, of *J* 1.5 Hz from δ 5.183 Hz, and of *J* 2.6 Hz from δ 2.062, and also caused δ 1.876 to change its coupling pattern to dddd, *J* 17.3, 5.5, 3.5, 1.4 Hz, suggesting it to be first order by agreement with the same *J* values from the coupled protons, respectively; J_{BX} 17.2, J_{AX} 10.5 or 9.6, $J_{A,B}$ 1.5 or 1.6, J_{2X} 5.0, $J_{2,3}$ 2.1, $J_{2,4}$ 3.5, $J_{2,B}$ 1.6, $J_{2,A}$ 1.5, $J_{5a,6}$ 10.2 or 10.3, $J_{6,CH}$ 6.3, $J_{6,CH}$ 3.7, $J_{5a,6}$ 3.4 or 3.5, $J_{5a,5b}$ 17.3, $J_{3,4}$ 10.2, $J_{3,5a}$ 5.6 or 5.5, $J_{4,5b}$ 2.6 or 2.3, $J_{4,5a}$ 1.4 or 1.5, and $J_{3,5b}$ 2.5, 2.6, or 2.2 Hz; ^{13}C-n.m.r. (50.2 MHz): δ 136.85 (CH=CH_2), 127.29 (C-3), 124.66 (C-4), 116.85 (CH=CH_2), 75.38 (CH_2OCH_3), 73.19 (C-2), 66.80 (C-6), 59.18 (CH_2OCH_3), and 26.97 (C-5); m.s. (c.i., CH_4, 100°): *m/z* 155 (67%, MH^+) and 153 (20%, $MH^+ - H_2$).

Anal. (h.r.c.i.m.s.) Calc. for $C_9H_{15}O_2$: 155.1072. Found: 155.1072.

*2-[2,2-Bis(ethoxy)ethyl]-6-methoxymethyl-5,6-dihydro-2*H*-pyrans* (**23** *and* **24**). — Compound **7** (560 mg, 3 mmol) in oxolane (12 mL) was treated with 2,2-diethoxyethylzinc chloride [prepared by adding M 2,2-diethoxyethylmagnesium bromide (3.15 mL) in oxolane to anhydrous $ZnCl_2$ (430 mg, 3.15 mmol) in oxolane (5 mL) at 0°] according to Method *B*. Chromatography on silica gel afforded **23** and **24** (ratio **23** to **24**, 3:1) as a colorless oil (460 mg, 79% based on **7** of 80% purity).

Compound **23**. R_F (20%, v/v, ethyl acetate–petroleum ether) 0.75; ν_{max}^{film} 3020 (C–CH), 2970, 2930, 2900, 2880 (CH), 1650 (C=C), 1185, 1120, 1100, 1050, and 1010 cm^{-1} (C–O); ^{1}H-n.m.r. (500 MHz): δ 5.989 (dddd, *J* 10.1, 5.6, 1.5, 1.5 Hz, H-3), 5.725 (dddd, *J* 10.1, 2.9, 2.9, 1.5 Hz, H-4), 4.999 (m, H-2), 4.712 (dd, *J* 3.1, 3.4 Hz, H-2′), 4.091 (dddd, *J* 11.5, 4.0, 4.0, 4.0 Hz, H-6), 3.843 (dddd, 2 H, *J* 9.7, 7.1, 7.1, 7.1 Hz, OCH), 3.524 (dddd, 2 H, *J* 9.7, 7.1, 7.1, 7.1 Hz, OCH), 3.46 (dd, *J* 5.8, 10.6 Hz, $CHOCH_3$), 3.370 (m, $CHOCH_3$), 3.386 (s, OCH_3), 2.137 (ddddd, *J* 17.7, 11.4, 2.3, 2.3, 2.2 Hz, H-5b), 1.894 (dddd, *J* 17.7, 5.5, 3.7, 1.5 Hz, H-5a), 1.221 (dd, 6 H, *J* 7.1, 7.1 Hz, CH_3), and 1.182 [m, 2 H, $CH_2CO(Et)_2$], irradiation at δ 4.999 caused a loss of *J* 1.5 Hz from δ 5.989, of *J* 2.9 Hz from δ 5.725, and of *J* 2.2 Hz from δ 2.137; ^{13}C-n.m.r. (125.7 MHz): δ 128.17 (C-3), 125.36 (C-4), 94.33 [$C(OC_2H_5)_2$], 74.86 (CH_2OCH_3), 66.47 (C-6), 65.08 (C-2), 63.04 (OCH_2CH_3), 59.05 (OCH_3), 37.89 (C-5), 26.51 [$CH_2C(OC_2H_5)_2$], and 15.20 (CH_3).

Compound **24**. ^{13}C-n.m.r. (125.7 MHz, 20% based on ^{13}C-n.m.r.): δ 129.30 (C-3), 123.42 (C-4), 100.29 [$C(OC_2H_5)_2$], 75.07 (CH_2OCH_3), 70.73 (C-6), 69.43

(C-2), 62.28 (OCH_2CH_3), 60.47 (OCH_3), 28.70 (C-5), 26.82 [$CH_2C(OC_2H_5)_2$], and 15.20 (CH_3); m.s. (c.i., CH_4, 100°): *m/z* 199.0 (20.1%, MH^+ − EtOH), 127.0 (100%), 103 (17.1%), and 170.9 (1.3%).

Anal. (h.r.c.i.m.s.) Calc. for $C_{13}H_{25}O_4$: 245.1753. Found: 245.1700. Calc. for $C_{11}H_{19}O_3$ (MH^+ − HOEt): 199.1330. Found: 199.1300.

*(2,3-Dideoxy-4,6-di-*O*-methyl-α-* (**25**) *and -β-*D-erythro-*hex-2-enopyranosyl)-benzene* (**26**). — Compounds **9** and **10** (5 mmol) in oxolane (25 mL) were treated with phenylzinc chloride [prepared from M phenylmagnesium bromide (5.5 mmol) in oxolane and anhydrous $ZnCl_2$ (715 mg, 5.25 mmol in oxolane (5 mL) at 0°] according to Method *B*. Silica gel chromatography afforded **25** and **26** as a pale-yellow oil (371 mg, 30% overall based on **9** and **10**) which was shown by ^{1}H-n.m.r. to be an ~1.0:1.0 mixture of **25** and **26**, R_F (30%, v/v, ethyl acetate–petroleum ether) 0.66 and 0.59; ν_{max}^{film} 3060, 3030 (C=CH), 2980, 2930, 2880, 2820 (CH), 1600 (C=C), and 1090 cm^{-1} (C–C); ^{1}H-n.m.r. (**25**; 500 MHz): δ 7.59–7.26 (m, 5 H, Ph), 6.140 (ddd, *J* 10.4, 2.0, 2.0 Hz, H-2′), 6.084 (ddd, *J* 10.4, 3.0, 1.6 Hz, H-3′), 5.28 (ddd, *J* 3.0, 2.0, 2.0 Hz, H-1′), 3.905 (dddd, *J* 7.5, 2.0, 2.0, 2.0 Hz, H-4′), 3.75–3.41 (m, 3 H, H-5′,6′,6″), 3.356 (s, OCH_3), and 3.425 (s, OCH_3); ^{1}H-n.m.r. (**26**; 500 MHz): δ 7.59–7.26 (m, 5 H, Ph), 5.996 (ddd, *J* 10.3, 2.4, 1.8 Hz, H-2′), 5.850 (ddd, *J* 10.3, 1.6, 1.5 Hz, H-3′), 5.157 (ddd, *J* 3.0, 2.4, 1.6 Hz, H-1′), 3.853 (dddd, 1 H, *J* 9, 3.0, 1.5, 1.5 Hz, H-4′), 3.75–3.41 (m, H-5′,6′,6′a,6′b), 3.438 (s, OCH_3), and 3.402 (s, OCH_3); ^{13}C-n.m.r. (**25**; 125.7 MHz, tentative assignments): δ 139.40, 129.61, 128.65, 128.27, 127.06, 126.46, 74.06 (C-1′), 71.88 (C-5′), 71.68 (C-4′), 70.21 (C-6′), 59.16 (OCH_3), and 56.46 (OCH_3); ^{13}C-n.m.r. (**26**; 125.7 MHz, tentative assignments): δ 141.15, 131.74, 128.37, 127.97, 127.15, 125.30, 77.49 (C-1′), 76.56 (C-5′), 72.67 (C-4′), 72.21 (C-6′), 59.39 (OCH_3), and 59.16 (OCH_3); m.s. (c.i., CH_4, 100°): *m/z* 235 (9%, MH^+), 263 (1.0%, $MC_2H_5^+$), 275 (1.0%, $MC_3H_5^+$), 203 (81%, MH^+ − MeOH), 161 (100%, MH^+ − H_3COCH_2CHO), and 157 (23%, MH^+ − C_6H_6).

Anal. (h.r.c.i.m.s.) Calc. for $C_{14}H_{19}O_3$: 235.1335. Found: 235.1300.

The mixture was separated by l.c. to afford pure **25**, R_T 24 min (20%, v/v, ethyl acetyl–hexane), $[\alpha]_D^{25}$ +19° (*c* 0.053, chloroform).

*1-(2,3-Dideoxy-4,6-di-*O*-methyl-α-* (**27**) *and -β-*D-erythro-*hex-2-enopyranosyl)naphthalene* (**28**). — 1-Naphthylzinc chloride was prepared by adding a solution of 0.298M 1-naphthylmagnesium bromide (6.0 mL) in 1:1 ether–benzene to anhydrous $ZnCl_2$ (0.236 g, 1.73 mmol) in oxolane (4.0 mL) at 0°, and the mixture was stirred for 30 min and then warmed to room temperature. To a solution of 1-*S*-acetyl-2,3-dideoxy-4,6-di-*O*-methyl-1-thio-α- and -β-D-*erythro*-hex-2-enopyranosides (**11**) (ratio of α to β, 7:43; 0.209 g, 0.900 mmol) in oxolane (50 mL) was added $Pd(PPh_3)_4$ (1.00 g, 0.866 mmol), and the mixture stirred at room temperature for 15 min. To this was added the solution of 1-naphthylzinc chloride and the mixture stirred for 6 h at room temperature, and then partitioned between water (10 mL) and ether. The aqueous layer was extracted with ether, followed by conventional workup to give a mixture of **27** and **28**, which was filtered through

silica gel and eluted with an ethyl acetate–hexane gradient. Pure **27** and **28** were obtained by semipreparative l.c. (0.040 g, 16%; ratio of **27** to **28**, 43:7); R_F (30%, v/v, ethyl acetate–hexane) 0.66, R_T 16.4 min (10%, v/v, ethyl acetate–hexane); $\nu_{max}^{CHCl_3}$ 3080 (C=CH), 3000, 2920, 2890, 2830 (CH), 1620 (C=C), 1110, and 1090 cm^{-1} (C–C).

Compound **27**. $[\alpha]_D^{25}$ +61° (*c* 0.0095, chloroform); ^{1}H-n.m.r. (200 MHz): δ 8.32–7.29 (m, 7 H, $C_{10}H_7$), 6.35–6.25 (ddd, *J* 10.3, 1.7, 1.7 Hz, H-2′), 6.23–6.13 (ddd, *J* 10.3, 3.1, 1.5 Hz, H-3′), 6.06–6.00 (m, H-1′), 4.13–4.02 (dd, *J* 8.0, 1.7 Hz, H-4′), 3.59–3.36 (m, H-5′,6′a,6′b), 3.48 (s, OCH_3), and 3.31 (s, OCH_3); ^{13}C-n.m.r. (**27**; 50.3 MHz): δ 134.3, 134.1, 132.3, 129.08, 127.64, 126.82, 126.29, 125.74, 127.71, 124.57 ($C_{10}H_7$), 129.71 (C-3′), 128.2 (C-2′), 71.75 (C-1′), 71.57 (C-5′), 71.26 (C-4′), 70.35 (C-6′), 59.26 (OCH_3), and 56.79 (OCH_3); m.s.e.i.: *m/z* 284 (18%, M^+), 210 (78%), 207 (78%), 179 (100%), and 127 (19%, $C_{10}H_7$).

Anal. (h.r.e.i.m.s.) Calc. for $C_{18}H_{20}O_3$: 284.1413. Found: 284.1407.

Compound **28**. ^{1}H-n.m.r. (200 MHz): δ 5.85–5.81 (m, H-1′); remaining peaks were buried under those of **27**.

*4-(2,3-Dideoxy-4,6-di-*O*-methyl-α-* (**29**) *and -β-*D-erythro-*hex-2-enopyranosyl)toluene* (**30**). — *p*-Tolylzinc chloride was prepared by adding 0.768M *p*-tolylmagnesium bromide (0.54 mL) in oxolane to anhydrous $ZnCl_2$ (0.056 g, 0.413 mmol) in oxolane (10 mL) at 0°, and the mixture stirred for 30 min, and then warmed to room temperature. To a solution of **11** (ratio of α to β, 7:93; 0.080 g, 0.344 mmol) in oxolane (10 mL) was added $Pd(PPh_3)_4$ (0.398 g, 0.344 mmol) and the mixture stirred at room temperature for 15 min. To this was added the solution of *p*-tolylzinc chloride and the resulting mixture stirred for 6 h at room temperature. Workup and chromatography as described for the prepration of **27** and **28** afforded **29** and **30** (0.045 g, 21%), $[\alpha]_D^{25}$ +37° (*c* 0.0095, chloroform); R_F (30%, v/v, ethyl acetate–hexane) 0.65, R_T (30%, v/v, ethyl acetate–hexane, 1.0 mL/min) 6.5 min; $\nu_{max}^{CHCl_3}$ 3050 (C=CH), 3000, 2920, 2890, 2820 (CH), 1620 (C=C), and 1100 cm^{-1} (C–C); ^{1}H-n.m.r. (**29**; 200 MHz): δ 7.35–7.08 (m, 4 H, Ph), 6.20–6.12 (ddd, *J* 10.4, 2.0, 1.8 Hz, H-2′), 6.12–6.02 (ddd, *J* 10.4, 2.6, 1.3 Hz, H-3′), 5.30–5.23 (br. s, H-1′), 3.87–3.86 (ddd, *J* 7.0, 1.7, 1.7 Hz, H-4′), 3.65–3.50 (m, H-5′,6′a,6′b), 3.43 (s, OCH_3), 3.36 (s, OCH_3), and 2.33 (s, CH_3); ^{1}H-n.m.r. (**30**; 200 MHz): δ 7.35–7.08 (m, 4 H, Ph), 6.05–5.96 (ddd, *J* 10.4, 2.0, 1.8 Hz, H-2′), 5.88–5.81 (ddd, *J* 10.4, 2.0, 1.5 Hz, H-3′), 5.17–5.12 (br. s, H-1′), 3.88–3.78 (m, H-4′), 3.78–3.60 (m, H-5,6′a,6′b), 3.44 (s, OCH_3), 3.40 (s, OCH_3), and 2.32 (s, CH_3); ^{13}C-n.m.r. (**29**; 50.3 MHz): δ 137.62, 136.44, 129.73, 129.00, 128.17, 126.46 (Ph), 74.08 (C-1′), 71.87 (C-5′), 71.72 (C-4′), 69.89 (C-6′), 59.24 (OCH_3), 56.56 (OCH_3), and 21.15 (CH_3); m.s.e.i.: *m/z* 248 (0.6%, M^+), 217 (1.2%), 203 (1.5%), 174 (100%), 159 (41%), and 143 (54%).

Anal. (h.r.e.i.m.s.) Calc. for $C_{15}H_{20}O_3$: 248.1413. Found: 248.1422.

*1-(2,3,6-Trideoxy-4-*O*-methyl-α-*L-erythro-*hex-2-enopyranosyl)-naphthalene* (**32**). — 1-Naphthylzinc chloride was prepared by adding 0.65M 1-naphthylmagnesium bromide (17.0 mL) in 12:5 oxolane–benzene to anhydrous $ZnCl_2$ (1.18

g, 8.66 mmol) in oxolane (7.0 mL) at 0°, and the mixture stirred for 30 min and then warmed to room temperature. To a solution of 1-*S*-acetyl-2,3,6-trideoxy-4-*O*-methyl-1-thio-β-L-*erythro*-hex-2-enopyranoside (**31**; 0.876 g, 4.33 mmol) in oxolane (50 mL) was added $Pd(PPh_3)_4$ (1.0 g, 0.866 mmol) and the mxiture stirred at room temperature for 15 min. To this was added the solution of 1-naphthylzinc chloride and the mixture stirred for 5 h, followed by partitioning with water (10 mL) and ether and exhaustive extraction of the aqueous layer with ether. Conventional processing was followed by chromatography of crude **32** on silica gel and elution with ethyl acetate–hexane, and then further purification by semipreparative l.c. afforded pure **32** (0.250 g, 23% based on **31**), $[\alpha]_D^{25}$ −64° (*c* 0.0060, chloroform); R_F (30%, v/v, ethyl acetate–hexane) 0.74, R_T (10%, v/v, ethyl acetate–hexane, 4.0 mL/min) 16 min; $\nu_{max}^{CHCl_3}$ 3080 (C=CH), 3000, 2920, 2890, 2830 (CH), 1620 (C=C), and 1110 cm^{-1} (C–O); ^{1}H-n.m.r. (200 MHz): δ 8.79–7.35 (m, 7 H, $C_{10}H_7$), 6.31–6.22 (d, *J* 10.1 Hz, H-2′), 6.22–6.15 (dd, *J* 10.1, 2.6 Hz, H-3′), 5.97–5.91 (br. s, whh 5.5 Hz, H-1′), 3.69–3.51 (m, 2 H, H-4′,5′), 3.48 (s, OCH_3), and 1.22–1.14 (d, *J* 5.61 Hz, CH_3); ^{13}C-n.m.r. (50.3 MHz): δ 132.99, 132.32, 130.30, 128.91, 128.60, 128.02, 126.27, 125.97, 124.29 ($C_{10}H_7$), 128.51 (C-3′), 128.36 (C-2′), 77.99 (C-1′), 70.53 (C-4′), 67.36 (C-5′), 56.52 (OCH_3), and 18.29 (C-6′); m.s.e.i.: *m/z* 254 (7.8%, M^+), 222 (1.3%), and 210 (100%).

Anal. (h.r.e.i.m.s.) Calc. for $C_{17}H_{18}O_2$: 254.1307. Found: 254.1309.

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ORGANOMETALLICS IN ORGANIC SYNTHESIS. APPLICATIONS OF A NEW DIORGANOZINC REACTION TO THE SYNTHESIS OF *C*-GLYCOSYL COMPOUNDS WITH EVIDENCE FOR AN OXONIUM-ION MECHANISM*

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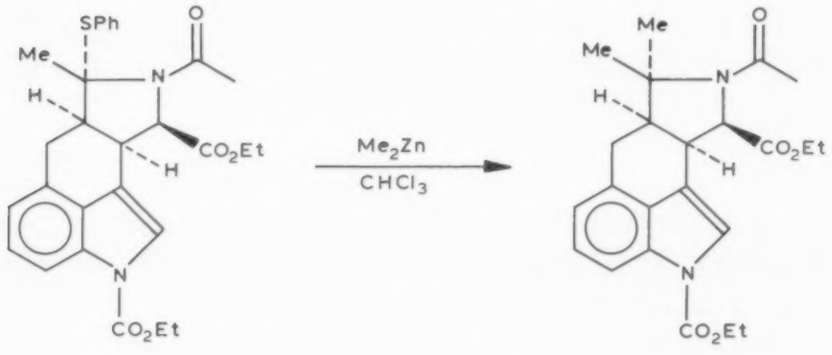
ABSTRACT

The mechanistic and stereochemical features of a new organozinc-based substitution process [heteroatom-C-(R^1,R^2)-SPh + R^3_2Zn → heteroatom-C-(R^1,R^2,R^3)], first discovered during a total synthesis of the alkaloid mycotoxin α-cyclopiazonic acid, are described. Phenyl thioglycosides were valuable substrates in studying the nature of this reaction process. Since these sulfur compounds are converted into *C*-glycosyl compounds with some degree of stereoselectivity, the organozinc chemistry does provide a new entry to these biologically active substances.

INTRODUCTION

During our investigations into the synthesis of the unique mycotoxin, α-cyclopiazonic acid, the need arose to replace a phenylthio group in **1** by a methyl group[1] in **2**. After numerous unsuccessful attempts with a wide variety of methylmetals, we finally discovered that dimethylzinc in chloroform effected this conversion in



1 2

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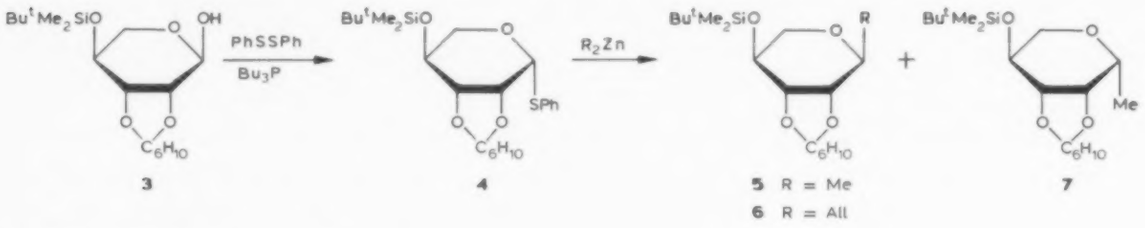
good yield. Even though a large excess of the diorganozinc reagent was employed, no products derived from a reaction at the carbonyl sites were observed, a consequence of the relatively weak nucleophilicity of organozinc reagents[2].

In order to further probe both the synthetic and mechanistic aspects of this new reaction, we have extended the zinc chemistry to several different phenyl thioglycosides. Our purpose in choosing carbohydrates as substrates was twofold: (a) these substrates were expected to provide valuable stereochemical information on the course of the zinc reaction; and (b) if the yields and stereoselectivity observed in this reaction were good, then a valuable new entry into an important class of natural product substances, the *C*-glycosyl compounds, would be at hand. Much intensive effort has been expended in devising new entries into the *C*-glycosyl compounds[3] over the past few years, primarily because of the significant biological activity exhibited by these special carbohydrate structures.



3 **4** **5** R = Me, **6** R = All **7**

RESULTS AND DISCUSSION

To begin our study of the aforementioned zinc reaction with carbohydrates as substrates, we examined first the reactions of phenyl 4-*O*-*tert*-butyldimethylsilyl-2,3-*O*-cyclohexylidene-1-thio-β-L-lyxopyranoside (**4**), a compound readily prepared by an oxidation–reduction condensation reaction[5] between the protected L-lyxose derivative[6] **3**, diphenyl sulfide, and tributylphosphine. The structure of **4** has been independently confirmed by a single-crystal X-ray analysis. The replacement of the anomeric hydroxyl group of **3** by the phenylthio group with apparent inversion of configuration was suggestive of an SN2-type mechanism. When a chloroform solution of **4** was subsequently treated with excess dimethylzinc, prepared from methyl iodide and a zinc–copper couple[7], in a Kimax tube for 12 h at 75°, a single, less polar product was obtained. To this product was assigned the structure **5**, based upon a detailed n.m.r. analysis *(vide infra)*.

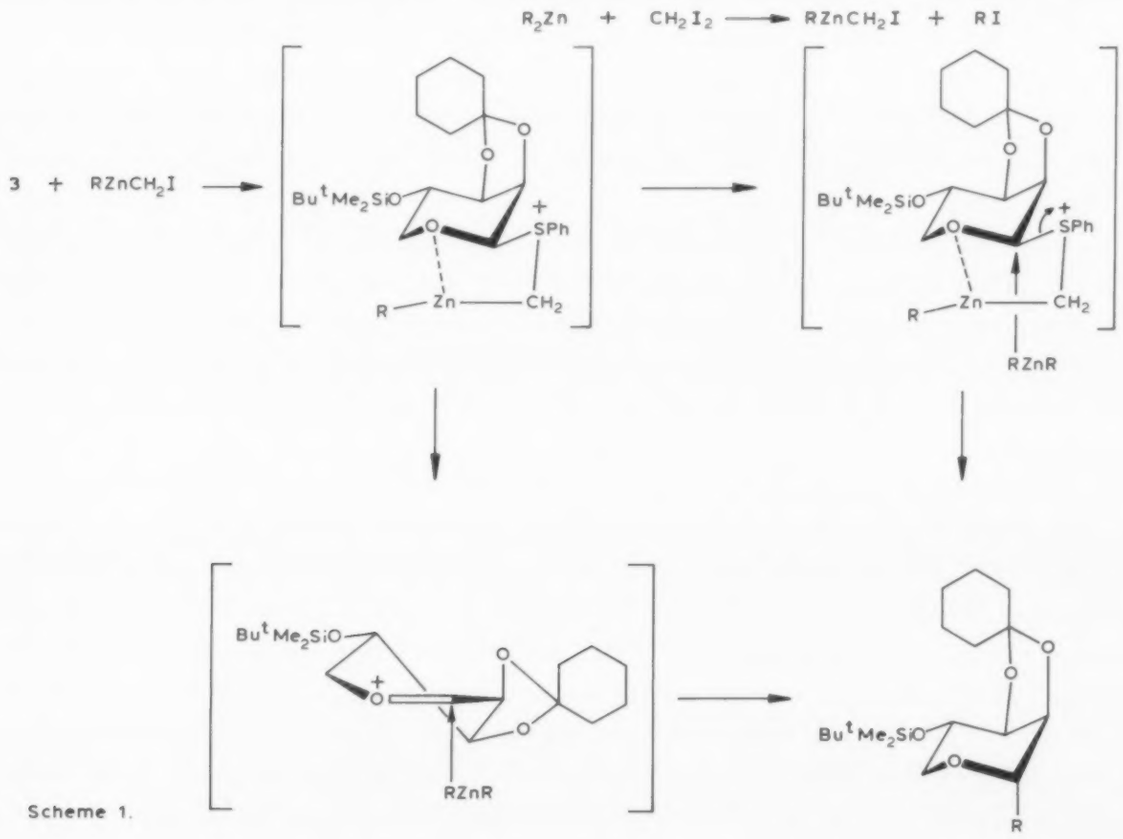
Interestingly, when the reaction just mentioned was carried out in toluene, benzene, or hexanes, in the absence of chloroform, no glycosylmethane was formed. Additionally, when a toluene solution of **4** was treated with five equivalents of diiodomethane and ten equivalents of commercially available diethylzinc for 2 h at 65°, a glycosylethane compound was obtained in a yield of 78%. Likewise, by substituting carbon tetrachloride for diiodomethane, the glycosylethane compound was again obtained, but under a milder set of reaction conditions (2 h at 35°).

Early on in our studies, we felt that the zinc reagent might be reacting with the phenyl thioglycoside through a ligand-type exchange process in which the

thiophilic zinc center might sufficiently tug on the sulfur atom to form an oxonium-ion intermediate. However, our findings regarding the necessity of the halocarbon additives does logically suggest that the dialkylzinc is performing a dual role. First, it reacts with diiodomethane or carbon tetrachloride (by a free radical pathway) to deliver a carbenoid[2,8]; subsequently, this zinc carbenoid interacts with the sulfur substituent to generate a sulfonium ion intermediate[9]. The formation of this intermediate may be additionally favored through complexation of the zinc atom with the ether oxygen atoms of the carbohydrate nucleus. Complexation of the zinc atom of the Simmons–Smith reagent with a hydroxyl group has, of course, been invoked previously to rationalize the *syn*-directing effect of an alcohol in cyclopropanation reactions[10].

Once the activated organozinc–sulfur complex has formed, it reacts with the excess diorganozinc reagent present in solution either by a direct displacement mechanism, or (better) it breaks down to a cyclic oxonium ion which then undergoes attack *via* the kinetically-preferred, axial-addition mode[11]. Thus, conformational energetics and the kinetic anomeric effect act synergistically to control the configuration resulting from the addition in the latter case (see Scheme 1).

As listed in Table I, the dimethyl-, diethyl-, and dipropyl-zinc reagents provided, within the limits of ^{1}H-n.m.r. and l.c. analysis, only the *C*-α-L-glycosyl compounds. The assignment of structure to these compounds was based on detailed spin–spin decoupling experiments carried out on the desilylated products. The anomeric proton of these α-L anomers exhibited a coupling constant of J 8.2–9.2



Scheme 1.

TABLE I

REACTIONS OF DIORGANOZINC REAGENTS WITH THE PHENYL THIOGLYCOSIDE **4**

Reagent R_2Zn (R)	*C-Glycosyl compounds (%)*[a]		*Yield (%)*
	α	*β*	
CH_3	>94	<6	72
CH_3CH_2	>94	<6	78
$CH_3CH_2CH_2$	>94	<6	76
$CH_3(CH_2)_2CH_2$	93	7	75
$C_2H_5CH(CH_3)$	64	36	72
$(CH_3)_2CH$	82	18	73
CH_2=CH–CH_2	60	40	35[b]

[a]A standard set of reaction conditions was adopted which consisted of treating **4** with the diorganozinc reagent (15 equiv.) and diiodomethane (8 equiv.) in toluene for 2 h at 40°. [b]The low yield in this case probably stems from our difficulty in preparing the pure diallylzinc reagent.

Hz with the neighboring pyran-ring proton[11]. The anomeric proton in the desilylated β-L anomers exhibited a coupling constant of J 1.9–2.4 Hz. The chemical shift of the C-5 axial-methylene proton was also found to differ considerably for the desilylated products of **5** and **7** (δ 3.58–3.75 and 3.03–3.34, respectively). Further proof of structure for the glycosylpropane compound was obtained by comparing it with an authentic sample generated by hydrogenating the previously known[12] α-L-glycosylpropene. With dibutylzinc, a 93:7 mixture of the α- and β-L anomers was obtained. The secondary alkylzinc reagents, prepared by reaction of the appropriate organolithium or Grignard reagent with freshly fused zinc chloride in ether, followed by distillation[2,13], proved somewhat less selective in their reactions with **4**. While the α-L anomer still preponderated, more of the β-L anomer was detected (Table I).

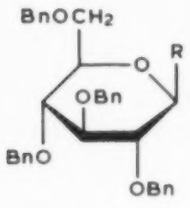
In order to test the applicability of this organozinc reaction to other carbohydrate substrates, as well as to further confirm our suspicions that this reaction was proceeding through an oxonium ion intermediate, we have examined the reaction of the additional phenyl thioglycosides listed in Table II. The phenylthio substituted derivatives of β- and α-D-glucose (**8** and **10**) provided us with an excellent opportunity to examine the effect of the configuration of the starting compound on that of the product. If an oxonium ion intermediate was being formed in the course of the organozinc-mediated reactions, then **10** and **8** would give rise to nearly identical product ratios. Indeed, as tabulated in Table II, the product ratios observed for the reactions of **10** and **8** with Me_2Zn–CH_2I_2 were quite similar. As should be noted, the major isomer is that arising from an axial-addition mode. On treating **8** with diethylzinc or diphenylzinc in the presence of diiodomethane, α- to β-ratio of anomers in the products was again found to be ~3:1. Thus, the nature of the diorganozinc reagent does not dramatically influence the product distribution. The lower level of stereoselectivity observed with this D-glucose derivative, as

TABLE II

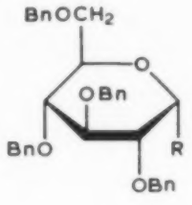
REACTIONS OF OTHER PHENYL THIOGLYCOSIDES WITH DIORGANOZINC REAGENTS

Starting phenyl thioglycoside	*Organozinc reagent*	*Reaction conditions*[a]		*Product*	*Ratio of α to β anomer*	*Yield (%)*
		Temp (°)	*Time (h)*			
8[b]	Me_2Zn	45	3.5	**29**	76:24	67
8[b]	Me_2Zn	5	72	**29**	77:23	76
8[b]	Et_2Zn	50	3	**30**	72:28	67
8[b]	Ph_2Zn	50	2	**28**	75:25	48
9[c]	Me_2Zn	90	12	**29**	67:33	24
9[c]	Me_2Zn	50	4		α-chloride[e]	44
10[c]	Me_2Zn	50	3	**29**	69:31	60
11[c]	Me_2Zn	50	4	**29**	73:27	55
12, 13[b]	Me_2Zn	40	3	**31**	84:16[d]	80
12, 13[b]	Ph_2Zn	50	1	**32**	81:19	40
14[b]	Me_2Zn	48	20	**15, 16**	37:63	91
21[f]	Et_2Zn	25	2	**33**	75:25	68

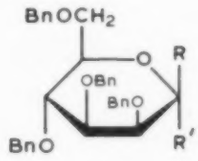
[a]These reactions were all carried out by use of 15 equiv. of the diorganozinc reagent and 8 equiv. of diiodomethane in toluene as solvent. [b]Ref. 5. [c]Ref. 14. [d]Product ratio assigned after debenzylation and conversion to the tetraacetates. [e]See text. [f]Ref. 15.



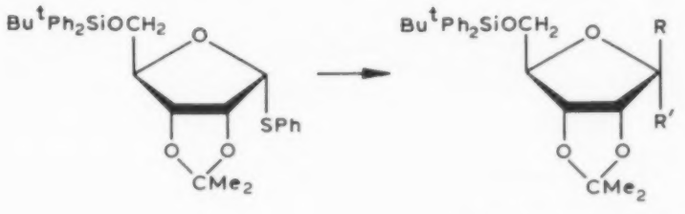
8 R = SPh
9 R = SBu



10 R = SPh
11 R = SBu



12 R = SPh, R′ = H
13 R = H, R′ = SPh



14

15 R = Me, R′ = H
16 R = H, R′ = Me

compared to that observed for the L-lyxose derivative, presumably reflects the ability of the 1,3-dioxolane ring in the latter to significantly shield the pyran ring from attack in the equatorial direction (*i.e.*, the concave-face attack is hindered).

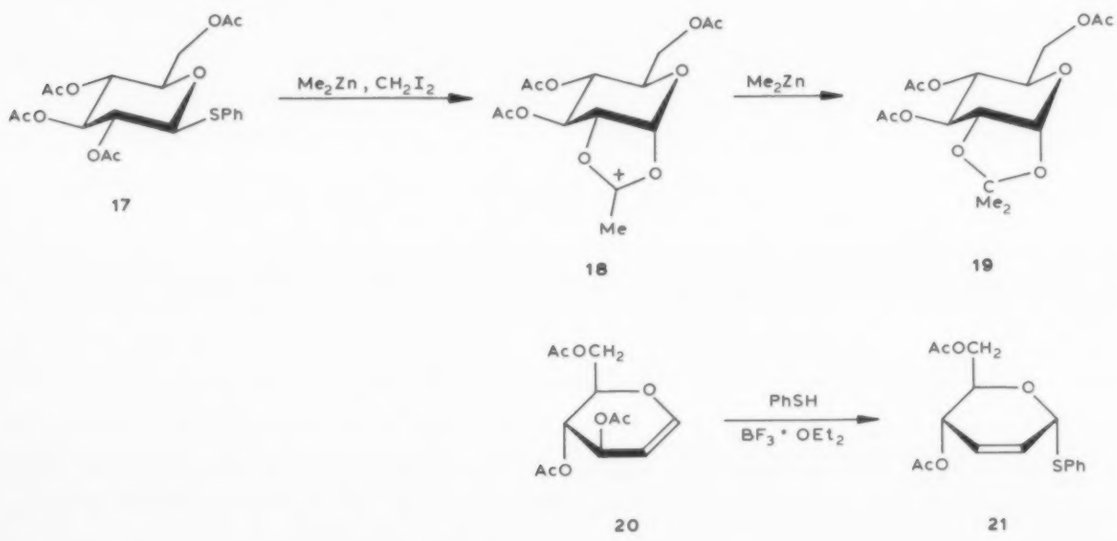
Interestingly, the butylthio derivatives **9** and **11** of D-glucose differed considerably in their reactivity towards Me_2Zn–CH_2I_2. Whereas the α anomer **11**

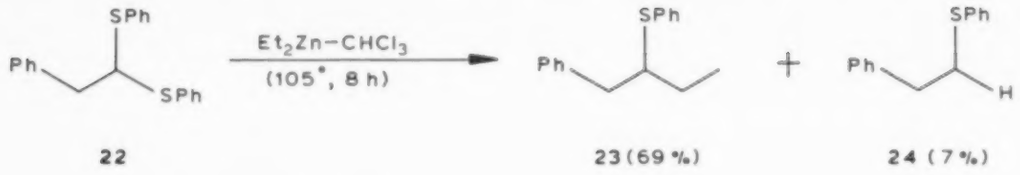
reacted within 4 h at 50° to provide a 73:27 mixture of α- and β-D-glucosylmethane, the β anomer **9** required heating for 12 h at 90° in order to generate even small amounts of the desired products. On treating **9** with Me_2Zn–CH_2I_2 for 4 h at 50°, followed by a workup with hydrochloric acid, only the corresponding glucosyl chloride could be isolated. Apparently, the sluggish character of **9** in the zinc reaction reflects both the poorer-leaving group ability of a butylsulfonium relative to a phenylsulfonium ion-group, as well as the inability of the lone pairs on the pyran-ring oxygen atom to participate in the cleavage process[11].

On treatment of a 1:1 mixture of the D-mannose-derived phenyl thioglycosides **12** and **13** with either dimethylzinc or diphenylzinc, the products of axial attack again preponderated. The presence of the β-axial benzyloxy group at C-2 may be responsible for the slight enhancement in axial selectivity relative to the D-glucose examples.

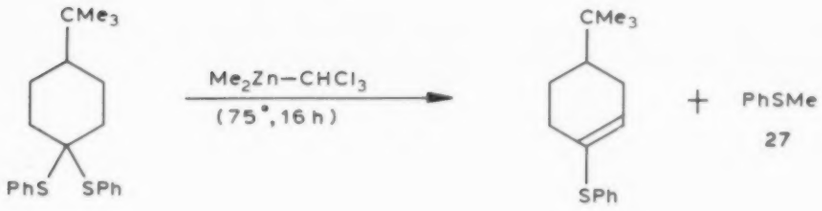
When the phenylthio derivative of α-D-ribose **14** was subjected to Me_2Zn–CH_2I_2, a mixture of furanosylmethanes was formed in excellent yield. To the major product was assigned a β-D configuration (**15**) based upon an examination of the chemical shift and coupling data of **15** and **16** vis-à-vis that reported for related compounds[16].

On exposing the *O*-acetylated derivative **17** of D-glucose to the standard reaction conditions, it was interesting to find that none of the expected glucosylmethane was formed. Instead, the 1,2-*O*-isopropylidene derivative of D-glucose **19** was isolated in 51% yield. This compound, whose structure was made apparent by ^{1}H-n.m.r. analysis, presumably resulted from attack of the C-2 acetate group on the anomeric center backside to the departing sulfur group. The resulting acyloxonium ion **18** then suffered attack by the dimethylzinc leading to the *O*-isopropylidene derivative. Not unexpectedly, the α anomer of **17** gave rise to a complex mixture of products. The zinc reaction was also applied to the phenylthio derivative **21** prepared from 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (**20**)

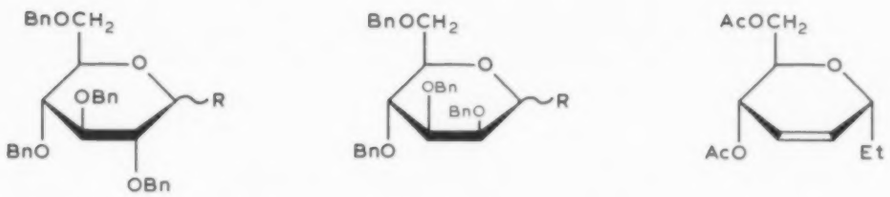




22 23 (69 %) 24 (7 %)



25 26 (43 %) 27



28 R = C_6H_5
29 R = Me
30 R = Et

31 R = Me
32 R = Ph

33

by Ferrier rearrangement[15]. In this case, the new alkyl group entered into the position α to the pyran-ring oxygen atom, and by literature comparisons the major anomer was found to have the α-D configuration[4] (**33**).

While we have attempted to extend the foregoing chemistry to another type of α-heteroatom containing sulfur system, the thioacetals rather complicated mixtures of products were found to be formed when these materials were exposed to diorganozinc reagents in the presence of various halocarbons. The bis(phenylthio)acetal **22** of phenylacetaldehyde reacted, for example, with diethylzinc in the presence of chloroform as solvent to give rise to the expected substitution product **23**, in which one of the phenylthio groups was replaced by an ethyl group. Additionally, some of the product of reduction **24** was isolated as well. In other cases, elimination of one of the thio groups to afford a vinyl sulfide was also observed, *e.g.*, **25** to give **26** and **27**. A recent report by Rodriguez and Nickon describes the use of similar methodology for the conversion of dithioacetals into vinyl sulfides[17].

In summary, the phenyl thioglycosides, when treated with diorganozinc reagents in the presence of halocarbon additives, lead to reasonable yields of *C*-glycosyl compounds. The resulting configuration does appear to be consistent with an axial attack on an oxonium-ion intermediate. The organozinc procedure thus offers a further addition to the rapidly growing number of new methods available for *C*-glycosyl construction[3,4].

TABLE III

^{1}H-N.M.R., I.R., M.S., AND H.R.M.S. DATA FOR THE *C*-GLYCOSIDE COMPOUNDS

Compound	*^{1}H-N.m.r.*[a]	*I.r.*	*M*
(4-*O*-*tert*-Butyldimethylsilyl-2,3-*O*-cyclohexylidene-L-lyxopyranosyl)-methane, α anomer (**5**)	3.97 (m, 1 H), 3.90 (m, 1 H), 3.71 (dd, 1 H, *J* 8.49, 5.05 Hz), 3.59 (m, 2 H), 3.27 (dt, 1 H, *J* 6.1, 2.02 Hz), 1.25–1.60 (m, 10 H), 1.15 (d, 3 H, *J* 6.1 Hz), 0.83 (s, 9 H), and 0.03 (s, 6 H)	2960, 2860, 1510, 1420, 1360 1250, 1190, 1090, 1040, 1010, 930, and 840[b]	3 2
-ethane, α anomer	4.03 (m, 1 H), 3.96 (m, 1 H), 3.80 (dd, 1 H, *J* 8.2, 5.1 Hz), 3.67 (m, 2 H), 3.15 (dt, 1 H, *J* 8.29, 4.04 Hz), 1.6 (m, 12 H), 0.98 (t, 3 H, *J* 6.94 Hz), 0.88 (s, 9 H), and 0.09 (s, 6 H)	2950, 1600, 1460, 1360,1250, 1090, 1050, 890, and 840[b]	3 3
(2,3-*O*-Cyclohexylidene-L-lyxopyranosyl)-propane α anomer	4.21 (m, 1 H), 3.97 (m, 1 H), 3.85 (m, 3 H), 3.19 (dt, 1 H, *J* 8.46, 3.56 Hz) 2.44 (d, 1 H, *J* 8.46 Hz), 1.60 (m, 14 H), and 0.93 (t, 3 H, *J* 6.99 Hz)	3580, 2950, 2850, 1520, 1460, 1370, 1200, 1160, 1110, 1080, 1035, 970, 920, and 830[b]	2 2

M.s.	*H.r.m.s.* (Anal.)
342 (M^+), 299, and 285	Calc. for $C_{18}H_{34}O_4Si$: 342.2226. Found: 342.2226.
356 (M^+), 327 ($M^+ - Et$)	Calc. for $C_{19}H_{36}O_9Si$: 356.2383. Found: 356.2384.
256 (M^+), 213 ($M^+ - Pr$)	Calc. for $C_{14}H_{24}O_4$: 256.1675. Found: 256.1674.

-butane, α anomer	4.21 (br s, 1 H), 3.97 (br d, 1 H, *J* 6.27 Hz), 3.85 (m, 3 H), 3.17 (dt, *J* 8.49, 3.44 Hz), 2.15 (d, 1 H, *J* 8.29 Hz), 1.7 (m, 10 H), 1.35 (m, 6 H), and 0.9 (t, 3 H, *J* 7.1 Hz)	3550, 3400, 2900, 2850, 1450, 1440, 1390, 1355, 1315, 1260, 1235, 1190, 1150 1100, 1060, 1040, 980, 905, and 880[b]	2
-butane, β anomer	4.04 (dd, 1 H, *J* 5.46, 2.22 Hz), 3.9 (m, 2 H), 3.8 (m, 1 H), 3.55 (dt, 1 H, *J* 5.86, 2.02 Hz), 3.07 (t, 1 H, *J* 10.81 Hz), 2.0 (d, 1 H, *J* 3.64 Hz), 1.77 (m, 10 H), 1.35 (m, 6 H), and 0.9 (t, 3 H, *J* 7.1 Hz)	3600, 3430, 2950 2850, 1450 1430, 1360, 1260, 1235, 1190, 1150, 1100, 1085, 1055, 1030, 930, and 900[b]	2
-1-methylpropane, α anomer	4.23 (m, 1 H), 4.06 (dd, 1 H, *J* 9.1, 5.25 Hz), 3.95 (m, 1 H), 3.75 (m, 2 H), 3.14 (dd, 0.5 H, *J* 9.3, 3.4 Hz), 3.07 (dd, 0.5 H, *J* 9.3, 5.25 Hz), 2.1 (m, 1 H), 1.6 (m, 10 H), and 1.3–0.9 (m, 9 H)	3600, 3420, 2920, 2850, 1450, 975, and 930[b]	2 2

270 (M^+)	Calc. for $C_{21}H_{40}O_4Si$: 384.2696. Found: 384.2697. (for the mixture of silyl ethers)
270 (M^+)	
270 (M^+) 237	Calc. for $C_{21}H_{40}O_4Si$: 384.2696. Found: 384.2692. (for the mixture of silyl ethers)

Table III (continued)

Compound	*^{1}H-N.m.r.*	*I.r.*[b]	*M*
-1-methylpropane, β anomer	4.17 (m, 1 H), 3.9 (m, 2 H), 3.8 (m, 2 H), 3.1 (dd, 1 H, *J* 8.9, 2.22), 3.03 (dt, 1 H, *J* 11.2, 2.02 Hz), 1.6 (m, 10 H), and 1.2–0.9 (m, 9 H)	3400, 2950, 2850, 1455, 1370, 1350, 1185, 1160, 1115, 1085, 1060, and 935[b]	2 2
-1-methylethane, α anomer	4.23 (br d, 1 H, *J* 6.49 Hz), 4.03 (dd, 1 H, *J* 8.95, 5.25 Hz), 3.95 (br d, 1 H, *J* 6.67 Hz), 3.72 (m, 2 H), 3.00 (dd, 1 H, *J* 9.09, 5.25 Hz), 2.10 (d, 1 H, *J* 8.49 Hz), 1.83 (m, 1 H), 1.6 (m, 10 H), 1.0 (d, 3 H, *J* 6.87 Hz), and 0.95 (d, 3 H, *J* 6.67 Hz)	3630, 3480, 2950, 2870, 1450, 1430, 1370, 1350, 1315, 1260, 1190 1155, 1090, 1060, 1035, 970, 905, and 850[b]	2 2
-1-methylethane, β anomer	4.17 (dd, 1 H, *J* 5.25, 2.36 Hz), 3.9 (m, 2 H), 3.78 (m, 1 H), 3.11 (dd, 1 H, *J* 9.4, 2.2 Hz), 3.03 (t, 1 H, *J* 11.11 Hz), 2.11 (d, 1 H, *J* 3.64 Hz), 2.05 (m, 2 H), 1.55 (m, 10 H), 1.05 (d, 3 H, *J* 6.67 Hz), and 0.97 (d, 3 H, *J* 6.67 Hz)	3600, 3400, 2930, 2890, 1450, 1360, 1345, 1315, 1260, 1240, 1190, 1156, 1105, 1085, 1065, 1015, 980, 960, 930, and 880[b]	2 2

M.s.	*H.r.m.s.* (Anal.)
270 (M^+) 237	
nd	
256 (M^+), and 213 (M^+ − iPr)	Calc. for $C_{20}H_{38}O_4Si$: 370.2540. Found: 370.2539. (for the mixture of silyl ethers)
256 (M^+) 213 (M^+ − iPr)	

(2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl)-methane, α anomer (**29**)	7.41–7.09 (m, 20 H), 5.00–4.41 (m, 8 H), 4.27 (quintet, 1 H, *J* 6.6 Hz), 3.86–3.51 (m, 6 H), and 1.29 (d, 3 H, *J* 6.6 Hz)	3040, 2930, and 1050[c]	4
β anomer (**29**)	7.42–7.08 (m, 20 H), 4.88 (s, 2 H), 4.86–4.49 (m, 6 H), 3.85–3.65 (m, 4 H), 3.48–3.46 (m, 2 H), 3.20 (t, 2 H, *J* 10.5 Hz), and 1.22 (d, 3 H, *J* 6.6 Hz)	3040, 2940, and 1050[c]	4
-ethane, α anomer (**30**)	7.40–7.06 (m, 20 H), 5.70–4.42 (m, 8 H), 3.97–3.87 (m, 1 H), 3.83–3.49 (m, 6 H), 1.71 (quintet, 2 H, *J* 7.4 Hz), and 1.14 (t, 3 H, *J* 7.4 Hz)	3040, 2930, and 1050[c]	4
-ethane, β anomer (**30**)	7.41–7.05 (m, 20 H), 4.96–4.42 (m, 6 H), 4.90 (s, 2 H), 3.83–3.51 (m, 4 H), 3.45–3.12 (m, 3 H), 1.97–1.85 (m, 2 H), and 1.00 (t, 3 H, *J* 7.4 Hz)	3040, 2930, and 1050[c]	4
-benzene. α,β anomers (**28**)	7.80–7.00 (m, 25 H), 5.24 (d, 1 H, *J* 4.6 Hz), 5.01–4.41 (m, 8 H), and 4.19–3.44 (m, 6 H)	3070, 3040, and 1045[c]	3

447 ($M^+ - C_6H_5CH_2$) Calc. for $C_{28}H_{31}O_5$: 447.2172. Found: 447.2171.

50c

447 ($M^+ - C_6H_5CH_2$) Calc. for $C_{28}H_{31}O_5$: 447.2172. Found: 447.2171.

50c

461 ($M^+ - C_6H_5CH_2$) Calc. for $C_{29}H_{33}O_5$: 461.2328. Found: 461.2327.

50c

461 ($M^+ - C_6H_5CH_2$) Calc. for $C_{29}H_{33}O_5$: 461.2328. Found: 461.2328.

50c

509 ($M^+ - C_6H_5CH_2$) Calc. for $C_{33}H_{33}O_5$: 509.2329. Found: 509.2327.

45c

Table III (continued)

Compound	*^{1}H-N.m.r.*	*I.r.*[b]	M
(2,3,4,6-Tetra-*O*-benzyl-D-mannopyranosyl)-methane, α,β anomers (**31**)	7.42–7.05 (m, 20 H), 4.86–3.43 (m, 7 H), and 1.21 (d, 3 H, *J* 6.3 Hz)	3040, 2940, 1450, and 1090[c]	4
-benzene, α anomer (**32**)	7.43–7.11 (m, 25 H), 5.03 (d, 1 H, *J* 4.9 Hz), 4.75–4.45 (m, 8 H), 4.08 (dd, 1 H, *J* 4.9, 3.1 Hz), 4.00–3.85 (m, 4 H), and 3.70 (dd, 1 H, *J* 6.6, 3.3 Hz)	3050, 2940, and 1090[c]	5
β anomer (**32**)	7.10–7.50 (m, 25 H), 4.94–4.35 (m, 9 H), and 4.26–3.55 (m, 6 H)	3040, 2950, and 1100[c]	5
16	7.68–7.32 (m, 10 H), 4.84 (d, 1 H, 6.0 Hz), 4.60 (dd, 1 H, *J* 5.4, 5.1 Hz), 4.22 (dq, 1 H, *J* 7.0, 4.0 Hz), 4.09 (t, 1 H, *J* 5.0 Hz), 3.74 (dd, 1 H, 11.0, 5.0 Hz), 3.66 (dd, 1 H, 11.0, 5.0 Hz), 1.49 (s, 3 H), 1.34 (s, 3 H), 1.28 (d, 3 H, *J* 6.1 Hz), and 1.03 (s, 9 H)	2950 and 1100[c]	3
15	7.75–7.33 (m, 10 H), 4.73 (dd, 1 H, *J* 6.4, 3.8 Hz), 4.25 (t, 1 H, *J* 6.1 Hz), 4.05–3.95 (m, 2 H), 3.77 (d, 1 H, *J* 3.9 Hz), 1.53 (s, 3 H), 1.33 (s, 3 H), 1.31 (d, 3 H, *J* 6.5 Hz), and 1.06 (s, 9 H)	2950, 1110, and 1060[c]	3

	M.s.	*H.r.m.s.* (Anal.)
nd	447 ($M^+ - C_6H_5CH_2$)	Calc. for $C_{28}H_{31}O_5$: 447.2172. Found: 447.2171.
90[c]	509 ($M^+ - C_6H_5CH_2$)	Calc. for $C_{33}H_{33}O_4$: 509.2329. Found: 509.2331.
90[c]	509 ($M^+ - C_6H_5CH_2$)	
	369 ($M^+ - Bu^t$)	Calc. for $C_{21}H_{25}O_4Si$: 369.1522. Found: 369.1524.
60[c]	369 ($M^+ - Bu^t$)	Calc. for $C_{21}H_{25}O_4Si$: 369.1522. Found: 369.1522.

(4,6-Di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)ethane, α anomer (**33**)	5.81 (d, 1 H, *J* 10.3 Hz), 5.72 (d, 1 H) 1 H, *J* 10.3 Hz), 5.25 (d, 1 H, *J* 8.8 Hz), 4.28–4.09 (m, 6 H), 3.71 (ddd, 1 H, *J* 8.8, 5.8, 2.6 Hz), 2.10 (s, 3 H), 2.08 (s, 3 H), 1.60 (qd, 2 H, *J* 7.4, 2.5 Hz), and 0.93 (t, 3 H, *J* 7.4 Hz)	2950, 1736, 1455, 1210, and 1080[c]	2
β anomer	5.92 (ddd, 10.5, 2.4 1.5 Hz), 5.78 (dt, 10.5, 2.4 Hz), 5.17–5.09 (m, 1 H), 4.22 (dd, 1 H, 11.8, 6.5 Hz), 4.18–4.08 (m, 2 H), 3.92 (td, 1 H, *J* 6.5, 3.5 Hz), 2.10 (s, 3 H), 2.09 (s, 3 H), 1.78–1.49 (m, 2 H), and 1.00 (t, 3 H, *J* 7.4 Hz)	2950, 1736, 1450, 1220, and 1090[c]	2
19	5.60 (d, 1 H, *J* 5.0 Hz), 5.19 (t, 1 H), *J* 3.3 Hz, 4.90 (dd, 1 H, *J* 9.6, 2.8 Hz), 4.22 (dd, 1H, *J* 12.0, 4.8 Hz), 4.19 (dd, 1 H, *J* 12.0, 3.0 Hz), 4.11 (ddd, 1 H, *J* 9.6, 4.8, 3.0 Hz), 2.11 (s, 3 H), 2.10 (s, 3 H), 2.09 (s, 3 H), 1.61 (s, 3 H), and 1.35 (s, 3 H)	2990, 1740, 1215, 1020[c]	3

[a]For a solution in (^{2}H)chloroform. [b]For a solution in chloroform. [c]For a film.

213 ($M^+ - C_2H_5$) Calc. for $C_{10}H_{13}O_5$: 213.0763. Found: 213.0763.

213 ($M^+ - C_2H_5$) Calc. for $C_{10}H_{13}O_5$: 213.0763. Found: 213.0758.

331 ($M^+ - CH_3$) Calc. for $C_{14}H_{19}O_9$: 331.1029. Found: 331.1037.

EXPERIMENTAL

General methods. — Melting points were recorded with a Thomas–Hoover melting point apparatus and are uncorrected. Optical rotations were determined with a Perkin–Elmer 241 polarimeter. I.r. spectra were recorded with a Perkin–Elmer 247 grating infrared spectrometer using the polystyrene absorption at 1601 cm^{-1} as a reference. ^{1}H-N.m.r. spectra were recorded with a Varian EM-390 (90 MHz) or a Bruker WH-300 (300 MHz) instrument using tetramethylsilane as an internal standard (δ 0.00). Low-resolution mass spectra were recorded with a LKB 9000 A GC-mass spectrometer and high-resolution mass spectra with a Varian MAT CH-5DF mass spectrometer. T.l.c. was performed on Merck precoated Silica gel 60 F 254 glass plates, layer thickness 0.25 mm, with fluorescent indicator. The spots were detected by staining with a solution of $(NH_4)_6MO_7O_{24} \cdot 4\ H_2O$ (16 g) and $Ce(SO_4) \cdot n\ H_2O$ (1 g) in 10% H_2SO_4 (500 mL). Liquid chromatography was performed on a Waters Associates instrument using a μ-Porasil column. Column chromatography was performed on silica gel (70–230 mesh) from EM Reagents. All reactions were carried out under an inert atmosphere of Ar or N_2.

General procedure. — An oven-dried, resealable tube was purged with a slow stream of N_2, and then charged with the thioglycoside as a solution in benzene or toluene (~50mM) and diiodomethane (8 equiv.). The zinc reagent (~15-fold excess) was added dropwise, and the tube was sealed and heated at 40–50° for several hours. The tube was cooled in an ice-bath, and the reaction was quenched by the dropwise addition of methanol until effervescence ceased. A 5% solution of HCl was added dropwise, and the resulting mixture was extracted with dichloromethane. The organic layer was washed with aqueous $NaHCO_3$ solution, dried ($MgSO_4$), concentrated, and chromatographed. The spectral data of the *C*-glycosyl compounds obtained are reported in Table III.

[*5-O-(*tert-*Butyldiphenylsilyl)-2,3-O-isopropylidene-β-*D- (**15**) *and -α-*D-*ribofuranosyl]methane* (**16**). — According to the general procedure, phenyl 5-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-1-thio-α-D-ribofuranoside (**14**) (28 mg, 54 μmol) was treated with diiodomethane (52 μL, 0.54 mmol) and dimethylzinc (51 mg) in benzene (1 mL) for 20 h at 48°. After workup, the crude mixture of **15** and **16** was chromatographed on silica gel with 5% ethyl acetate–hexane as eluent to give 13.2 mg of the less polar isomer **15**, and 7.7 mg of the more polar isomer **16** (91% yield, ratio α:β 37:63).

Anal. (mixture of **15** and **16**) Calc. for $C_{25}H_{34}OSi$: C, 70.38; H, 8.03. Found: C, 70.30; H, 7.89.

*(2,3,4,6-Tetra-*O*-benzyl-α,β-*D*-glucopyranosyl)benzene* (**28**). — According to the general procedure, phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**8**) (22 mg, 35 μmol) was treated with diiodomethane (22 μL, 8 equiv.) and diphenylzinc (77 mg, 10 equiv.) in benzene (0.7 mL) for 2 h at 50°. After quenching the reaction, the crude mixture was chromatographed on silica gel with 20% ethyl acetate–hexane as eluent to give a mixture (10 mg) of the α- and β-D-gluco-

pyranosylbenzenes **28** (48%). Integration of the ^{1}H-n.m.r. signals of the mixture showed that the α to β ratio of anomers was 3 to 1. The assignment of the α-D configuration to the major anomer was confirmed by conversion into the corresponding tetraacetate and comparison with an authentic sample prepared as described earlier[18]. The presence of the minor β-D anomer was confirmed by comparison of its ^{1}H-n.m.r. spectrum with the spectrum of an authentic sample prepared from 2,3,4,6-tetra-*O*-acetyl-β-D-(glucopyranosyl)benzene[18] by acetate cleavage and benzylation.

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HIGHLY STEREOSELECTIVE *C*-α-D-RIBOFURANOSYLATION. REACTIONS OF D-RIBOFURANOSYL FLUORIDE DERIVATIVES WITH ENOL TRIMETHYLSILYL ETHERS AND WITH ALLYLTRIMETHYLSILANE*

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ABSTRACT

2,3,5-Tri-*O*-methyl-D-ribofuranosyl fluoride (**6**), 2,3-di-*O*-benzyl-5-*O*-methyl-D-ribofuranosyl fluoride (**7**), and 5-*O*-benzyl-2,3-di-*O*-methyl-D-ribofuranosyl fluoride (**8**) were obtained in 57 (**6α**, 15; and **6β**, 42), 87 (**7α**, 22; and **7β**, 65), and 85.5 (**8α**, 35.5; and **8β**, 50%) yields, respectively, from the corresponding OH-1 derivatives by the reaction with *N,N*-diethyl-1,1,2,3,3,3-hexafluoropropylamine, adduct of hexafluoropropene with diethylamine. These fluorides and 2,3,5-tri-*O*-benzyl-D-ribofuranosyl fluoride (**5**) reacted with isopropenyl trimethylsilyl ether, (*Z*)-1-ethyl-1-propenyl trimethylsilyl ether, and allyltrimethylsilane, in the presence of boron trifluoride·diethyl etherate to give the corresponding 1-D-ribofuranosyl-2-propanones, 2-D-ribofuranosyl-3-pentanones, and 3-D-ribofuranosyl-1-propenes in good yields. *C*-Acetonylation was confirmed to afford the α-D anomer as the initial product, and the α-D anomer was isomerized into the corresponding β-D anomer to give a mixture. The *C*-allylation reaction gave only the α-D anomer. *C*-Pentanonylation, however, gave a mixture of diastereoisomers that could not be isolated. All reactions afforded almost the same results starting with either α- or β-D-ribofuranosyl fluoride. No reaction of the β anomer of **5** with 1-isopropyl-2-methyl-1-propenyl trimethylsilyl ether took place.

INTRODUCTION

Glycosyl fluorides have been shown to be excellent glycosyl donors[2,3] and subsequently have been used for glycosylation by several groups[4–11]. We have also reported the reactions of 2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl fluoride with isopropenyl trimethylsilylether[12,13], allyltrimethylsilane[1], and cyanotrimethylsilane[1].

*Synthetic studies by the use of fluorinated intermediates. Part 3. For Part 2, see ref. 1.

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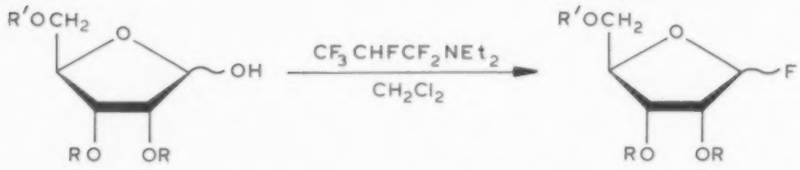
The first two reactions were shown to proceed with a remarkably high stereoselectivity to give preponderantly the α-D anomer. The last reaction, in contrast, afforded, as the initial products, isonitrile derivatives that were then subjected to isomerization into the corresponding cyanide derivatives, thus proceeding with low stereoselectivity. On the basis of the high stereoselectivity of the first two reactions, we investigated the reaction of some other D-ribofuranosyl fluoride derivatives with enol trimethylsilyl ethers and allyltrimethylsilane, and the results are described herein.

RESULTS AND DISCUSSION

Preparation of D-*ribofuranosyl fluoride derivatives.* — 2,3,5-Tri-*O*-benzyl-D-ribofuranosyl fluoride (**5**) was prepared by the treatment of 2,3,5-tri-*O*-benzyl-D-ribofuranose (**1**) with *N,N*-diethyl-1,1,2,3,3,3-hexafluoropropylamine (Ishikawa reagent; the adduct of hexafluoropropene with diethylamine) as previously reported[13,14]. 2,3,5-Tri-*O*-methyl- (**6**), 2,3-di-*O*-benzyl-5-*O*-methyl- (**7**), and 5-*O*-benzyl-2,3-di-*O*-methyl-D-ribofuranosyl fluoride (**8**) were prepared by treatment with



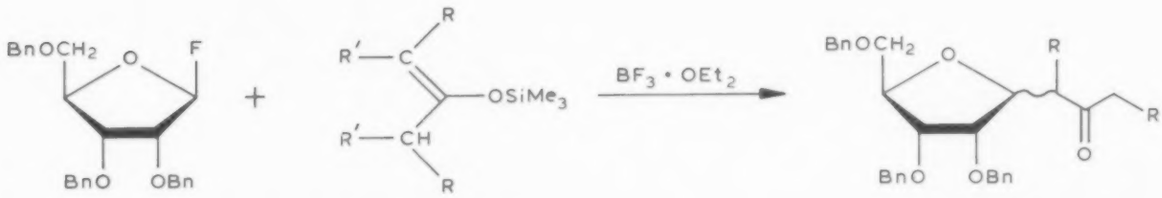
1 R = R′ = Bn
2 R = R′ = Me
3 R = Bn, R′ = Me
4 R = Me, R′ = Bn

5 R = R′ = Bn
6 R = R′ = Me
7 R = Bn, R′ = Me
8 R = Me, R′ = Bn

the Ishikawa reagent (1.5 mol. equiv.) with 2,3,5-tri-*O*-methyl-[15] (**2**), 2,3-di-*O*-benzyl-5-*O*-methyl- (**3**), and 5-*O*-benzyl-2,3-di-*O*-methyl-D-ribofuranose (**4**), respectively. All of these reactions, except that of **2**, proceeded smoothly in dichloromethane at room temperature to give **7** in 87% (22% of **7**α and 65% of **7**β) and **8** in 85% (35.5% of **8**α and 50% of **8**β) yield. The reaction of **2** was accompanied by undesirable discoloration to give **6** in ~40% yield. The yield was improved up to 57% (15% of **6**α and 42% of **6**β) by decreasing the proportion of the Ishikawa reagent to 1–1.1 mol. equiv. An attempt at permethylation of methyl β-D-ribofuranoside[16] by the Hakomori method[17] was unsuccessful, giving methyl 2,3,5-tri-*O*-methyl-β-D-ribofuranoside in ~10% yield only. The reaction with methyl iodide–pulverized sodium hydroxide in dimethyl sulfoxide[18] unexpectedly resulted in a 40% yield at most, in spite of several trials; this might be due to the preparation of pulverized sodium hydroxide on a preparative scale. The method of Wallenfelds *et al.*[19] using silver oxide–methyl iodide in *N,N*-dimethylformamide was approp-

riate, giving the permethylated β-D-ribofuranoside in ~80% yield. Compounds **3** and **4** were prepared from methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside[20] by methylation (methyl iodide–sodium hydride) or benzylation (benzyl bromide–sodium hydride), followed by *O*-deisopropylidenation with aqueous methanol–*p*-toluenesulfonic acid, benzylation or methylation, and hydrolysis with hydrochloric acid in aqueous 1,4-dioxane.

The structure of the D-ribofuranosyl fluoride derivatives, **6α**, **6β**, **7α**, **7β**, **8α**, and **8β** was confirmed by comparing the ^{1}H-n.m.r. and ^{19}F-n.m.r. spectra with those of **5** (α and β anomer)[13,14]. A characteristic difference was observed between the ^{19}F-n.m.r. spectra of the α and β anomers: the α anomers gave a quartet with larger splitting widths ($J_{1,F}$ 52–62, $J_{2,F}$ 19–22 Hz), and the β anomers a doublet ($J_{1,F}$ 51–58 Hz) with fine structures of small splitting width (3.5–4 Hz). These fine structures were apparently a quintet which might result from the overlapping of a doublet and a triplet ($J_{2,F}$, $J_{3,F}$, and $J_{4,F}$). This corresponds well to the difference observed between the ^{19}F-n.m.r. spectra of the 2,3,5-tri-*O*-acyl-D-ribofuranosyl fluoride anomers[21].



9 R = R′ = H
10 R = Me, R′ = H
11 R = R′ = Me

12 R = H
13 R = Me

Reactions of some D-*ribofuranosyl fluoride derivatives with trimethylsilyl compounds*. — These reactions were performed with isopropenyl trimethylsilyl ether[22] (**9**), (*Z*)-1-ethyl-1-propenyl trimethylsilyl ether[23] (**10**), 1-isopropyl-2-methyl-1-propenyl trimethylsilyl ether[24] (**11**), and allyltrimethylsilane (**15**). All reactions were induced by the catalysis of boron trifluoride·diethyl etherate, which has been effective[1,12,13] in the reactions of **5** with **9** or **15**, in diethyl ether and dichloromethane in the presence of molecular sieves at room temperature (see Table I). The reaction of the β anomer of **5** with **9** was complete within 5 min and gave 4,7-anhydro-5,6,8-tri-*O*-benzyl-1,3-dideoxy-D-*altro*-2-octulose [1-(2,3,5-tri-*O*-benzyl-α-D-ribofuranosyl)-2-propanone][12,13] **12α** (Table I). In view of the excellent reactivity of **5β**, this compound was treated with **10** and **11**. The reactivity of **10** was found to be lower compared with that of **9** (Table I). However, the reaction in dichloromethane was clearly improved to give 5,8-anhydro-6,7,9-tri-*O*-benzyl-1,2,4-trideoxy-4-*C*-methyl-D-3-nonulose [2-(2,3,5-tri-*O*-benzyl-D-ribofuranosyl)-3-pentanone] (**13**) in 92% yield (Table I). Compound **13** was a mixture of diastereoisomers, hardly separable, giving only a trace amount of isomerically pure compound. In this case, the

TABLE I

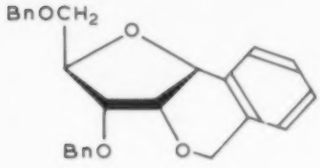
REACTION OF D-RIBOFURANOSYL FLUORIDES (**5, 6, 7,** AND **8**) WITH ENOL TRIMETHYLSILYL ETHERS (**9, 10,** AND **11**) AND WITH ALLYLTRIMETHYLSILANE (**15**)[a]

Fluoride	*Me_3Si cpd.*	*Solvent*	*Reaction time (min)*	*$BF_3 \cdot OEt_2$ (mol. equiv.)*	*Product yield (%) (α:β[b])*		*Recovery yield (%)*
5β[c]	**9**	Et_2O	5	0.05	**12**	94.6 (20:1)	
5β	**10**	Et_2O	30	0.05	**13**	52.1	39.7
5β	**10**	Et_2O	50	0.1	**13**	61.3	27
5β	**10**	CH_2Cl_2	50	0.05	**13**	91.9	6.7
5β	**11**	Et_2O	120	0.1		(no reaction)	
5β	**11**	Et_2O	120	1	**14**	23.4	38.5
5β	**11**	CH_2Cl_2	120	0.5		(no reaction[d])	
5β[e]	**15**	CH_2Cl_2	30	0.05	**16**	93.1 (100:0)	
5α[c]	**9**	Et_2O	20	0.05	**12**	89 (20:1)	
5α[e]	**15**	CH_2Cl_2	30	0.05	**17**	93.4 (100:0)	1.8
6β	**9**	Et_2O	5	0.05	**20**	90.2 (1.8:1)	
6β	**9**	Et_2O	15	0.025	**20**	39.0 (100:0)	42.0
6β	**10**	CH_2Cl_2	15	0.05	**21**	76.4	
6β	**15**	CH_2Cl_2	17	0.05	**16**	88.4 (100:0)	
7β	**9**	Et_2O	15	0.05	**22**	34.6 (100:0)	60.6[f]
7β	**9**	Et_2O	6	0.2	**22**	83.0 (100:0)	7.9[f]
7β	**10**	CH_2Cl_2	15	0.05	**23**	89.4	
7β	**15**	CH_2Cl_2	20	0.05	**18**	90.3 (100:0)	
7α	**9**	Et_2O	15	0.05	**22**	27.0 (100:0)	65.7[f]
7α	**15**	CH_2Cl_2	20	0.05	**18**	90.3 (100:0)	
8β	**9**	Et_2O	10	0.025	**24**	42.4 (100:0)	50.3
8β	**15**	CH_2Cl_2	10	0.05	**19**	84.2 (100:0)	
8α	**9**	Et_2O	15	0.05	**24**	58.5 (4.5:1)	35.7
8α,β[g]	**9**	Et_2O	7	0.2	**24**	85.6 (1.3:1)	6.5
8α,β[g]	**15**	CH_2Cl_2	10	0.05	**19**	75.2 (100:0)	

[a]All reactions were performed by the use of a D-ribofuranosyl fluoride derivative (100 mg) and a trimethylsilated compound (2 mol. equiv.) in a solvent (2 mL) in the presence of 4A molecular sieves (1 g) at room temperature. [b]The ratio was estimated by ^{1}H-n.m.r. spectra ($-CH_2CO-$ and $-COCH_3$). [c]Data from refs. 12 and 13. [d]The formation of **14** was deduced on the basis of t.l.c. [e]Data from ref. 1. [f]Deterioration of $BF_3 \cdot OEt_2$ might have brought about extremely low yield, but stereoselectivity was clearly noticed. [g]~1:1 Mixture of **8α** and **8β**.

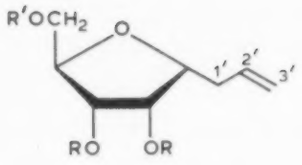
stereoselectivity was lowered considerably by an anomerization similar to that of **5β** with **9**, in which **12α** was isomerized into **12β** by extending the reaction time or performing the reaction in dichloromethane[12,13]. No reaction of **5β** with **11** took place, as the expected *C*-glycosyl compounds would bear a tertiary carbon atom, a stereochemically crowded structure, but compound **14**, which probably arose from an intramolecular Friedel–Crafts reaction, was obtained from the reaction mixture*. This compound was also obtained from the treatment of **5β** with less nucleophilic

*The structure of compound **14** will be reported in a forthcoming publication.

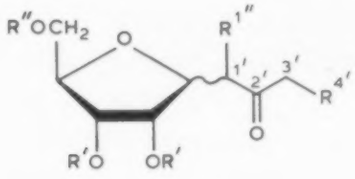


14

15



16 R = R′ = Bn
17 R = R′ = Me
18 R = Bn, R′ = Me
19 R = Me, R′ = Bn



20 R = H, R′ = R″ = Me
21 R = R′ = R″ = Me
22 R = H, R′ = Bn, R″ = Me
23 R = R″ = Me, R′ = Bn
24 R = H, R′ = Me, R″ = Bn

agents, such as trimethylsilylacetylene and ethyl trimethylsilylacetate[25], and by treatment[26] of **5β** with $BF_3 \cdot OEt_2$.

The reaction of **5α** with **9** also gave **12α** in a high yield with high stereoselectivity similarly to the reaction of **5β** with **9**. Moreover, both of the reactions of **5β** and **5α** with allyltrimethylsilane (**15**) gave the same product, *i.e.*, 4,7-anhydro-5,6,8-tri-*O*-benzyl-1,2,3-trideoxy-D-*altro*-oct-1-enitol [3-(2,3,5-tri-*O*-benzyl-α-D-ribofuranosyl)-1-propene][1] (**16**) (Table I); no β-D anomer was detected at all. Compound **16** was not susceptible to isomerization, in contrast to **12α** which was isomerized into **12β** in dichloromethane solution. Such preponderant formation of **12α** and **16** from either **5β** or **5α** led to the conclusion that these reactions proceeded *via* an SN1 mechanism by way of a D-ribofuranosyl cation[1,12,13].

It is very interesting that both of the fluorides **5β** and **5α** underwent an SN1-like reaction to give a *C*-glycosyl compound composed of an α-D anomer almost completely. The preferred formation of α-D-glycosyl compounds in the pyranose series is widely explained by the anomeric effect[27]. As the furanose ring tends to have a considerable flexibility due to pseudorotation, it has been difficult to explain the stereoselectivity of the furanosylation reaction by the anomeric effect[28]. The mutual stability of a pair of anomers has been discussed on the basis of such a steric effect as the 1,2- or 1,3-nonbonded group interaction. Generally, the 1,2-*trans* (β-D-*ribo*) is more stable energetically than the 1,2-*cis* relationship (α-D-*ribo*), although the difference may not be great[29]. As the proportion of α to β in **12** at equilibrium was ~1:2.5 (refs. 12, 13), the β-D anomer is a little more stable than the α-D anomer, and the steric factors are not controlling the attacking direction of

the nucleophile. A similar stereoselectivity was observed when the reaction was performed in dichloromethane (Table I) and, thus, a stereocontrol by solvent effect is difficult to take into consideration. The formation of **14** by the treatment of **5β** with **11** (23% yield) (Table I), and by the treatment of **5β** with $BF_3 \cdot OEt_2$ (0.5 and 1.5 mol. equiv.) in dichloromethane and ether (83 and 47%, respectively)[26] led to assumption of an anchimeric effect, by interaction of the phenyl group of the *O*-benzyl substituent toward a C-1 carbenium ion, as a potential factor of such stereocontrol. Participation of the phenyl group in synthetic organic chemistry is well known[30,31], although not in the field of carbohydrate chemistry. A study with Dreiding models demonstrated that both phenyl groups of the 2- and 5-*O*-benzyl substituents can participate in the interaction with the C-1 carbenium ion; these correspond to Ar-5 and Ar-7 participation[30]. Precise evaluation of the mutual strength of the interaction is, however, difficult. In order to confirm the participation of the 5-*O*-benzyl group in the α-D-ribofuranosylation, **7** (no benzyl group at O-5 but at O-2), **8** (no benzyl group at O-2 but at O-5), and **6** (no benzyl group at O-2, 3, and 5) were prepared and treated with **9**, **10**, and **15** (Table I). Compound **6β** with **9** gave 1-(2,3,5-tri-*O*-methyl-D-ribofuranosyl)-2-propanone (**20**) in a good yield, but with a low stereoselectivity (α:β, 1.8:1); one half the amount of $BF_3 \cdot OEt_2$ gave almost only the α anomer, but the reaction was not complete. Treatment of **20α** thus obtained with ~1 mol. equiv. of $BF_3 \cdot OEt_2$ showed the almost complete conversion into the β anomer after 10 min (^{1}H-n.m.r.), thus indicating that the reaction affords initially the α-D-glycosyl compounds and that the α anomer is isomerized into the β anomer at a rate higher than that of the isomerization of **12α** into **12β**. Treatment of **6β** with **10** gave 2-(2,3,5-tri-*O*-methyl-D-ribofuranosyl)-3-pentanone (**21**) also in a high yield (proportion of isomers not established), and with **15** gave 3-(2,3,5-tri-*O*-methyl-α-D-ribofuranosyl)-1-propene (**17**) as the sole product (Table I), similar to the stereoselectivity observed in the reaction of **5β** with **15**.

Treatment of **7β** with **9**, **10**, and **15** similarly gave 1-(2,3-di-*O*-benzyl-5-*O*-methyl-α-D-ribofuranosyl)-2-propanone (**22α**), 2-(2,3-di-*O*-benzyl-5-*O*-methyl-D-ribofuranosyl)-3-pentanone (**23**) (a mixture of isomers), and 3-(2,3-di-*O*-benzyl-5-*O*-methyl-α-D-ribofuranosyl)-1-propene (**18**), respectively, in good yield (Table I). The reaction of **8β** with **9** gave 1-(5-*O*-benzyl-2,3-di-*O*-methyl-α-D-ribofuranosyl)-2-propanone (**24α**) preponderantly in the initial stage, and that with **15** also gave 3-(5-*O*-benzyl-2,3-di-*O*-methyl-α-D-ribofuranosyl)-1-propene (**19**) in a high yield (Table I).

The α-D-ribofuranosyl fluoride derivative **7α** also gave the corresponding α-D-glycosyl compounds **22α** and **18** preponderantly in the treatment with **9** and **15**, respectively (Table I). Treatment of **8α** and 8α,β (1:1 mixture of **8α** and **8β**) with **9** gave a mixture of **24α** and **24β** (Table I). The large amount of unchanged **8α** (nearer to the initial stage of the reaction) and of **24α** suggests also that the reaction gave the α-D-ribofuranosyl compound preponderantly. Treatment of **8α,β** with **15** also gave **19** as the sole product.

The structures of the 1-D-ribofuranosyl-2-propanones **20α**, **20β**, **22α**, **24α**,

and **24β** were determined by ^{1}H-n.m.r. spectroscopy by comparison with compounds[12,13] **12α** and **12β**, and those of the 3-D-ribofuranosyl-1-propenes **17, 18,** and **19** by comparison[1] with **16***.

Since the change from *O*-benzyl to *O*-methyl groups made no difference, the participation of the phenyl group of *O*-benzyl substituents may be neglected as a potential factor of stereoselectivity. The BF_3-catalyzed reaction of D-ribofuranosyl fluorides with trimethylsilylated nucleophiles was confirmed to proceed very efficiently *via* an SN1-like mechanism with an almost 100% formation of α-D-ribofuranosyl compounds. An alternative stereocontrol by anchimeric effect may exist through the ether oxygen atom, since anchimeric participation by benzyloxy and methyloxy groups is well known[33].

EXPERIMENTAL

General methods. — The melting point was determined with a Yanagimoto Micro-Melting-point apparatus, and is uncorrected. Specific rotations were measured with a JASCO DIP-4 polarimeter. I.r. spectra were recorded with a Hitachi 285 spectrophotometer. ^{1}H-N.m.r. spectra were recorded with a JEOL JNM-FX 200 (200 MHz) and Nicolet NT-360 (360 MHz) spectrometer, and ^{13}C-n.m.r. spectra with a JEOL JNM-FX 200 (50 MHz) spectrometer, for solutions in $CDCl_3$ with tetramethylsilane as the internal standard. ^{19}F-N.m.r. spectra were recorded with a Hitachi R-24 F spectrometer for solutions in $CDCl_3$ with trifluoroacetic acid as an external standard. The Ishikawa reagent (commercial name; hexafluoropropylene–diethylamine) and allyltrimethylsilane were purchased from Tokyo Chemical Industry, Co., Ltd. and Aldrich Chem. Co., respectively. The solvents used were purified and dried according to the usual procedures. 2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl fluoride[13,14] (**5β**), 2,3,5-tri-*O*-methyl-D-ribofuranose[15] (**2**), methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside[20], 2-propenyl trimethylsilyl ether[22] (**9**), (*Z*)-1-ethyl-1-propenyl trimethylsilyl ether[23] (**10**), and 1-isopropyl-2-methyl-1-propenyl trimethylsilyl ether[24] (**11**) were respectively prepared according to the methods reported. Flowing column chromatography was performed on Kieselgel 60 (Merck, Art. 9385) in benzene–ethyl acetate or hexane–ethyl acetate.

Methyl 5-O-benzyl-2,3-di-O-methyl-β-D-ribofuranoside and 5-O-benzyl-2,3-di-O-methyl-D-ribofuranose (**4**). — To a solution of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (5 g, 24 mmol) in oxolane (40 mL) under an N_2 atmosphere, was added NaH (1.3 g, 27 mmol; petroleum ether content, 55%). The solution was stirred until the evolution of H_2 ceased, and then was treated with tetrabutylammonium iodide (90 mg, 0.24 mmol) and benzyl bromide (6 mL, 50 mmol) for 3 h with stirring. The mixture was treated with silica gel (Wakogel C-300; 1.6 g), which was then filtered off and well washed with dichloromethane. The combined

*The structure of **16** has been identified with that of a known compound[32], but the citation in a previous paper[1] is incorrect.

filtrate and washings were dried ($MgSO_4$) and evaporated to give a syrup, which was then distributed between hexane (30 mL) and acetonitrile (30 mL). The acetonitrile layer was evaporated to a syrup which was subjected to chromatography separation in a 40:1 benzene–ethyl acetate system to give methyl 5-*O*-benzyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (7.1 g, 98.6% yield). This (7 g, 24 mmol) was treated in 4:1 methanol–water (150 mL) with *p*-toluenesulfonic acid monohydrate (0.5 g, 2.6 mmol) for 2 h under reflux. After being cooled, the acidic solution was made neutral with Amberlite IRA-410 (OH) anion-exchange resin. After filtration, the solution was evaporated to a syrup which was chromatographed with ethyl acetate to give the starting material (1.6 g, 23% recovery yield) and methyl 5-*O*-benzyl-β-D-ribofuranoside (3.3 g, 50% yield). This (2.6 g, 10 mmol) was treated with methyl iodide (12.5 mL, 200 mmol) and Ag_2O (2.3 g, 100 mmol) in *N,N*-dimethylformamide (50 mL) in the dark with stirring at room temperature for 4 days. The mixture was filtered off, and the residue washed with methanol. The combined filtrate and washings were evaporated to a syrup which was again methylated as just described. The resulting syrup was chromatographed in 1:1 hexane–ethyl acetate to give methyl 5-*O*-benzyl-2,3-di-*O*-methyl-β-D-ribofuranoside (2.3 g, 80% yield), syrup, $[\alpha]_D^{28}$ +10.3° (*c* 1.3, chloroform); ^{1}H-n.m.r. (200 MHz): δ 3.36, 3.40, 3.49 (3 s, 9 H, 3 CH_3), 3.54 (dd, 1 H, $J_{4,5}$ 5.9, $J_{5,5'}$ 10.5 Hz, H-5), 3.65 (dd, 1 H, $J_{4,5'}$ 3.9 Hz, H-5′), 3.71 (d, 1 H, $J_{2,3}$ 4.9 Hz, H-2), 3.86 (dd, 1 H, $J_{3,4}$ 6.8 Hz, H-3), 4.21 (ddd, 1 H, H-4), 4.61 (s, 2 H, CH_2Ph), 4.92 (s, 1 H, H-1), and 7.24–7.32 (bs, 5 H, C_6H_5); ^{13}C-n.m.r. (50 MHz): δ 55.04 (OCH_3), 58.22 (2 OCH_3), 71.47, 73.16, 80.16, 80.48, 81.92 (C-2–5 and CH_2Ph), 105.42 (C-1), 127.45, 128.17, and 138.15 (C_6H_5).

Anal. Calc. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.92; H, 7.80.

A solution of the aforementioned methyl β-D-ribofuranoside (2.3 g, 8.1 mmol) in 5:1 1,4-dioxane–M HCl was heated at reflux for 2 h. After being cooled, it was poured into a saturated $NaHCO_3$ aqueous solution to neutralize the acid. The solution was evaporated to give a solid which was extracted with acetone several times. The combined extracts were evaporated into a syrup which was chromatographed with 1:1 hexane–ethyl acetate to give **4** (1.7 g, 78% yield), syrup, $[\alpha]_D^{26}$ +44.6° (*c* 2.70, chloroform); ^{1}H-n.m.r. (200 MHz): δ 3.38, 3.42, 3.48, 3.49 (4 s, 6 H, 2 OCH_3 of two anomers), 3.38–3.72 (m, 3 H, H-5,5′ and OH), 3.80–4.32 (m, 3 H, H-2,3,4), 4.48, 4.56 (AB type, *J* 11 Hz), 4.53, 4.62 (AB type, *J* 12 Hz) (2 H, CH_2Ph of two anomers), 5.24–5.34 (overlapped bs and bd, 1 H, H-1 of two anomers), and 7.27–7.33 (bs, 5 H, C_6H_5) (proportion of anomers ~3:2); ^{13}C-n.m.r. (50 MHz): δ 58.22, 58.40, 58.49 (OCH_3), 70.18, 73.34, 73.42, 79.72, 79.96, 80.04, 80.19, 80.25, 82.96 (C-2–5, CH_2Ph), 127.39, 127.65, 127.74, 128.32, 137.33, and 137.71 (C_6H_5).

Anal. Calc. for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.36; H, 7.42.

*Methyl 2,3-di-*O*-benzyl-5-*O*-methyl-β-*D*-ribofuranoside and 2,3-di-*O*-benzyl-5-*O*-methyl-*D*-ribofuranose* (**3**). — Treatment of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (5 g, 24 mmol) with methyl iodide (3 mL, 48 mmol) in a similar way

to that described for **4** but without tetraethylammonium iodide gave methyl 2,3-*O*-isopropylidene-5-*O*-methyl-β-D-ribofuranoside (5.3 g, 100% yield). This (5 g, 23 mmol) was *O*-deisopropylidenated as described for **4** to give the starting material (1.6 g, 32% recovery yield) and methyl 5-*O*-methyl-β-D-ribofuranoside (1.7 g, 42% yield). This (1.6 g, 9 mmol) was treated with benzyl bromide (2.2 mL, 19 mmol) as described for **4** to give syrupy methyl 2,3-di-*O*-benzyl-5-*O*-methyl-β-D-ribofuranoside (2.8 g, 87% yield), $[\alpha]_D^{30}$ +21.1° (*c* 1.3, chloroform); ^{1}H-n.m.r. (200 MHz): δ 3.31 (s, 3 H, OCH_3), 3.35 (s, 3 H, OCH_3), 3.37 (dd, 1 H, $J_{5,5'}$ 10.3, $J_{4,5}$ 7.3 Hz, H-5), 3.52 (dd, 1 H, $J_{4,5'}$ 3.6 Hz, H-5′), 3.81 (d, 1 H, $J_{2,3}$ 4.9 Hz, H-2), 3.93 (dd, 1 H, $J_{3,4}$ 7.1 Hz, H-3), 4.30 (ddd, 1 H, H-4), 4.42, 4.58 (2 H, AB type, *J* 12 Hz, CH_2Ph), 4.57, 4.64 (2 H, AB type, *J* 11.5 Hz, CH_2Ph), 4.89 (s, 1 H, H-1), and 7.25–7.36 (bs, 5 H, C_6H_5); ^{13}C-n.m.r. (50 MHz): δ 50.44, 54.55 (2 OCH_3), 67.65, 67.76, 69.57, 73.77, 74.97, 75.55 (C-2–5 and CH_2Ph), 101.72 (C-1), 123.13, 123.24, 123.68, and 133.10 (C_6H_5).

Anal. Calc. for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.23; H, 7.26.

The compound (2.7 g, 7.5 mmol) just described was hydrolyzed as described for **4** to give syrupy **3** (2.1 g, 81% yield), $[\alpha]_D^{27}$ +54.8° (*c* 2.78, chloroform); ^{1}H-n.m.r. (200 MHz): δ 3.29, 3.31 (2 s, 3 H, OCH_3), 3.30–3.60 (m, 2 H, H-5,5′), 3.80–4.35 (m, 4 H, H-2,3,4 and OH), 4.38–4.75 (m, 4 H, 2 CH_2Ph), 5.27–5.35 (m, 1 H, H-1), and 7.24–7.32 (m, 10 H, 2 C_6H_5) (proportion of anomers, ~4:3); ^{13}C-n.m.r. (50 MHz): δ 58.98, 59.24 (2 OCH_3), 72.14, 72.43, 72.61, 72.78, 77.48, 77.59, 77.77, 80.30, 80.63, 80.74 (C-2–5 and 2 CH_2Ph), 96.09, 100.11 (2 C-1), 127.62, 127.77, 128.23, 128.29, 137.36, 137.45, 137.65, and 137.74 (C_6H_5).

Anal. Calc. for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.44; H, 7.06.

5-O-Benzyl-2,3-di-O-methyl-α- (**8α**) *and -β-D-ribofuranosyl fluoride* (**8β**). — To a solution of **4** (1.7 g, 6.3 mmol) in dichloromethane (80 mL), under an N_2 atmosphere in a three-necked, round-bottomed flask, was added the Ishikawa reagent (1.8 mL, 1.6 mol. equiv.) through a syringe and the mixture was stirred at room temperature for 45 min. The reaction was quenched with aqueous, saturated $NaHCO_3$ solution (20 mL) and the organic layer separated. The aqueous layer was extracted with dichloromethane (3 × 30 mL) which was combined with the organic layer and dried ($MgSO_4$). After filtration, the solution was evaporated to a syrup which was subjected to chromatography in 2:1 hexane–ethyl acetate to give **8β** (0.86 g, 50% yield) and **8α** (0.61 g, 35% yield).

Compound **8α**. Syrup, $[\alpha]_D^{28}$ +40.1° (*c* 2.73, chloroform); ^{1}H-n.m.r. (200 MHz): δ 3.43 (s, 3 H, OCH_3), 3.51 (s, 3 H, OCH_3), 3.57 (d, 2 H, H-5), 3.77–3.88 (m, 2 H, H-2,3), 4.45–4.60 (m, 3 H, H-4 and CH_2Ph), 5.79 (dd, 1 H, $J_{1,F}$ 66.2, $J_{1,2}$ 2.9 Hz, H-1), and 7.31–7.36 (m, 5 H, C_6H_5); ^{13}C-n.m.r. (50 MHz): 58.57, 58.63 (2 OCH_3), 70.07, 73.48, 77.33, 84.45 (C-3–5 and CH_2Ph), 81.25 (d, $J_{C\text{-}2,F}$ 22.0 Hz, C-2), 108.1 (d, $J_{C\text{-}1,F}$ 233 Hz, C-1), 127.72, 127.71, 128.35, and 137.60 (C_6H_5); ^{19}F-n.m.r.: δ 52.45 (dd, $J_{1,F}$ 53.1, $J_{2,F}$ 18.9 Hz).

Anal. Calc. for $C_{14}H_{19}FO_4$: C, 62.21; H, 7.08. Found: C, 61.90; H, 7.03.

Compound **8β**. Syrup, $[\alpha]_D^{27}$ +54.8° (*c* 2.78, chloroform); ^{1}H-n.m.r. (200

MHz): δ 3.41 (s, 3 H, OCH_3), 3.51 (s, 3 H, OCH_3), 3.61 (dd, 1 H, $J_{4,5}$ 5.4, $J_{5,5'}$ 11.0 Hz, H-5), 3.72 (dd, 1 H, $J_{4,5'}$ 3.4 Hz, H-5′), 3.88–4.00 (m, 2 H, H-2,3), 4.20–4.25 (m, 1 H, H-4), 4.57, 4.64 (2 H, AB type, *J* 12.2 Hz, CH_2Ph), 5.73 (d, 1 H, $J_{1,F}$ 62.6 Hz, H-1), and 7.26–7.35 (m, 5 H, C_6H_5); ^{13}C-n.m.r. (50 MHz): δ 58.46, 58.69, (2 OCH_3), 70.39, 73.33, 79.16, 82.20 (C-3–5 and CH_2Ph), 81.15 (d, $J_{C-2,F}$ 29.3 Hz, C-2), 111.79 (d, $J_{C-1,F}$ 224 Hz, C-1), 127.50, 128.23, and 137.97 (C_6H_5); ^{19}F-n.m.r.: δ 37 (d-quintet, $J_{1,F}$ 51.3 Hz, overlapped dt with spacing of 3.3 Hz).

Anal. Calc. for $C_{14}H_{19}FO_4$: C, 62.21; H, 7.08. Found: C, 62.38; H, 7.18.

2,3,5-Tri-O-methyl-α- (**6α**) *and -β-*D*-ribofuranosyl fluoride* (**6β**). — 2,3,5-Tri-*O*-methyl-D-ribofuranose (**2**; 2.31 g, 12 mmol) was treated with the Ishikawa reagent (2.3 mL, 1.1 mmol) as described for **8α,β** to give **6β** (0.78 g, 33.5% yield) and **6α** (0.24 g, 10.5% yield).

Compound **6α**. Syrup, $[\alpha]_D^{20}$ +49.0° (*c* 1.35, chloroform); ^{1}H-n.m.r. (200 MHz): δ 3.38 (s, 3 H, OCH_3), 3.46 (s, 3 H, OCH_3), 3.50 (d, 2 H, $J_{4,5}$ 3.7 Hz, H-5), 3.53 (s, 3 H, OCH_3), 3.7–3.9 (m, 2 H, H-2,3), 4.48 (bs, 1 H, H-4), and 5.79 (dd, 1 H, $J_{1,F}$ 66.2, $J_{1,2}$ 3.0 Hz, H-1); ^{13}C-n.m.r. (50 MHz): δ 58.57, 58.63, 59.36 (3 OCH_3), 72.69, 77.18, 84.39 (C-3–5), 81.24 (C-2, $J_{C-2,F}$ 20.5 Hz), and 108.12 (C-1, $J_{C-1,F}$ 233 Hz); ^{19}F-n.m.r.: δ 52.2 (dd, $J_{1,F}$ 61.6, $J_{2,F}$ 22.3 Hz).

Anal. Calc. for $C_8H_{15}FO_4$: C, 49.48; H, 7.78. Found: C, 49.27; H, 7.61.

Compound **6β**. Syrup, $[\alpha]_D^{20}$ +81.0° (*c* 1.68, chloroform); ^{1}H-n.m.r. (200 MHz): δ 3.42 (s, 3 H, OCH_3), 3.45 (s, 3 H, OCH_3), 3.52 (dd, 1 H, $J_{4,5}$ 5.6, $J_{5,5'}$ 10.8 Hz, H-5), 3.53 (s, 3 H, OCH_3), 3.63 (dd, 1 H, $J_{4,5'}$ 3.4 Hz, H-5′), 3.90–3.96 (m, 2 H, H-2,3), 4.15–4.30 (m, 1 H, H-4), and 5.71 (d, 1 H, $J_{1,F}$ 63.0 Hz, H-1); ^{13}C-n.m.r. (50 MHz): δ 58.46, 58.72; 59.33 (3 OCH_3), 73.22, 79.23, 82.00 (C-3–5), 81.11 (d, $J_{C-2,F}$ 30.8 Hz, C-2), and 111.80 (d, $J_{C-1,F}$ 224.2 Hz, C-1); ^{19}F-n.m.r.: δ 37 (d-quintet, $J_{1,F}$ 58.1 Hz, overlapped dt with a spacing of 3.6 Hz).

Anal. Calc. for $C_8H_{15}FO_4$: C, 49.48; H, 7.78. Found: C, 49.76; H, 7.59.

2,3-Di-O-benzyl-5-O-methyl-α- (**7α**) *and -β-*D*-ribofuranosyl fluoride* (**7β**). — Treatment of **3** (2.10 g, 6.1 mmol) with the Ishikawa reagent (1.58 mL, 1.5 mol. equiv.) as described for **8α,β** gave **7β** (1.374 g, 65.1% yield) and **7α** (0.463 g, 21.9% yield); the reaction time was 50 min in this case, and the chromatography was performed with 40:1 benzene–ethyl acetate.

Compound **7α**. Syrup, $[\alpha]_D^{27}$ +39.5° (*c* 1.33, chloroform); ^{1}H-n.m.r. (200 MHz): δ 3.27 (s, 3 H, OCH_3), 3.28 (dd, 1 H, $J_{4,5}$ 3.9, $J_{5,5'}$ 10.7 Hz, H-5), 3.36 (dd, 1 H, $J_{4,5'}$ 3.9 Hz, H-5′), 3.74–3.94 (bd, 1 H, H-2), 3.91 (bs, 1 H, H-3), 4.46 (bs, 1 H, H-4), 4.61, 4.74 (2 H, AB type, *J* 12.2 Hz, CH_2Ph), 4.61, 4.70 (2 H, AB type, *J* 12.2 Hz, CH_2Ph), 5.68 (dd, 1 H, $J_{1,F}$ 65.4, $J_{1,2}$ 3.3 Hz, H-1), and 7.30–7.35 (bs, 10 H, 2 C_6H_5); ^{13}C-n.m.r. (50 MHz): δ 59.27 (OCH_3), 72.17, 72.49, 72.69, 74.19, 84.80 (C-3–5 and 2 CH_2Ph), 78.67 (d, $J_{C-2,F}$ 20.5 Hz, C-2), 108.41 (d, $J_{C-1,F}$ 233 Hz, C-1), 127.65, 127.77, 127.85, 128.00, 128.23, 128.32, 137.28, and 137.83 (2 C_6H_5); ^{19}F-n.m.r.: δ 52.0 (dd, $J_{1,F}$ 55.4, $J_{2,F}$ 18.9 Hz).

Anal. Calc. for $C_{20}H_{23}FO_4$: C, 69.35; H, 6.69. Found: C, 69.45; H, 6.81.

Compound **7β**. M.p. 43.9–44.0° (pentane), $[\alpha]_D^{26}$ +67.9° (*c* 2.01,

chloroform); ^{1}H-n.m.r. (200 MHz): δ 3.36 (s, 3 H, OCH_3), 3.46 (dd, 1 H, $J_{4,5}$ 5.4, $J_{5,5'}$ 11.0 Hz, H-5), 3.59 (dd, 1 H, $J_{4,5'}$ 3.2 Hz, H-5′), 3.97 (t, 1 H, $J_{2,3}$ 4.4, $J_{2,F}$ 4.2 Hz, H-2), 4.07 (ddd, 1 H, $J_{3,4}$ 8.3, $J_{3,F}$ 2.7 Hz, H-3), 4.40 (ddt, 1 H, $J_{4,F}$ 4.3 Hz, H-4), 4.46, 4.57 (2 H, AB type, *J* 12 Hz, CH_2Ph), 4.64 (s, 2 H, CH_2Ph), 5.65 (d, 1 H, $J_{1,F}$ 63.2 Hz, H-1), and 7.21–7.37 (m, 10 H, 2 C_6H_5); ^{13}C-n.m.r. (50 MHz): δ 59.24 (OCH_3), 72.69, 72.81, 76.92, 82.00, 82.06 (C-3–5 and 2 CH_2Ph), 78.75 (d, $J_{C\text{-}2,F}$ 30.8 Hz, C-2), 112.35 (d, $J_{C\text{-}1,F}$ 224 Hz, C-1), 127.77, 127.82, 128.12, 128.23, 128.32, 128.38, 137.19, and 137.30 (2 C_6H_5); ^{19}F-n.m.r.: δ 35.7 (d-quintet, $J_{1,F}$ 51.3 Hz, overlapped dt with a spacing of 3.4 Hz).

Anal. Calc. for $C_{20}H_{23}FO_4$: C, 69.35; H, 6.69. Found: C, 69.52; H, 6.78.

1-[2,3,5-Tri-O-methyl-α- (**20α**) *and -β-*D*-ribofuranosyl]-2-propanone* (**20β**). — To **6β** (100 mg, 0.52 mmol) and molecular sieves 4A (1 g) in a 30-mL, two-necked, round-bottomed flask under an N_2 atmosphere were added in turn, through a syringe, diethyl ether (2 mL) and isopropenyl trimethylsilyl ether (**9**, 0.163 mL, 1.03 mmol) and, through a microsyringe, $BF_3 \cdot OEt_2$ (3.2 μL, 25.8 μmol). After stirring for 5 min at room temperature, the reaction was quenched with aqueous saturated $NaHCO_3$ solution (2 mL). The solids were filtered off and well washed with acetone. The combined filtrate and washings were evaporated to dryness, and the residue was crushed and extracted with acetone. The extract was evaporated to a syrup which was chromatographed in 2:1 hexane–ethyl acetate to give **20** (110 mg, 90% yield; α:β, 1.8:1). Further chromatography gave **20α** (first fraction) and **20β** (5–10 mg).

Compound **20α**. Syrup, $[\alpha]_D^{23}$ +13.5° (*c* 0.93, chloroform); ν_{max}^{NaCl} 1715 (C=O) cm^{-1}; ^{1}H-n.m.r. (200 MHz): δ 2.18 (s, 3 H, H-3′), 2.79 (dd, 1 H, $J_{1,1'}$ 6.3, $J_{1',1''}$ 17 Hz, H-1′), 2.90 (dd, 1 H, $J_{1,1''}$ 6.8 Hz, H-1″), 3.39 (s, 3 H, OCH_3), 3.43 (dd, 1 H, $J_{4,5}$ 4.6, $J_{5,5'}$ 10.5 Hz, H-5), 3.46 (s, 6 H, 2 OCH_3), 3.54 (dd, 1 H, $J_{4,5'}$ 3.4 Hz, H-5′), 3.78 (dd, 1 H, $J_{2,3}$ 4.6, $J_{3,4}$ 6.6 Hz, H-3), 3.93 (t, 1 H, $J_{1,2}$ 4.6 Hz, H-2), 4.02 (ddd, 1 H, H-4), and 4.50 (dt, 1 H, H-1); ^{13}C-n.m.r. (50 MHz): δ 30.66 (C-3′), 43.64 (C-1′), 58.54, 59.33, 59.68 (3 OCH_3), 73.01, 75.81, 78.91, 79.43, 82.00 (C-1–5), and 207.17 (C-2′).

Anal. Calc. for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 57.15; H, 8.55.

Compound **20β**. Syrup, $[\alpha]_D^{22}$ −12.9° (*c* 0.85, chloroform), ν_{max}^{NaCl} 1715 (C=O) cm^{-1}; ^{1}H-n.m.r. (200 MHz): δ 2.17 (s, 3 H, H-3′), 2.67 (d, 2 H, $J_{1,1'}$ 6.3 Hz, H-1′), 3.36 (s, 3 H, OCH_3), 3.40 (s, 3 H, OCH_3), 3.43 (s, 3 H, OCH_3), 3.38–3.53 (m, 3 H, H-2,5,5′), 3.73 (t, 1 H, $J_{2,3}$ 4.9, $J_{3,4}$ 4.7 Hz, H-3), 4.08 (q, 1 H, $J_{4,5}$ 4.6 Hz, H-4), and 4.31 (q, 1 H, $J_{1,2}$ 6.1 Hz, H-1); ^{13}C-n.m.r. (50 MHz): δ 30.54 (C-3′), 47.66 (C-1′), 57.76, 58.00, 59.36 (3 OCH_3), 72.96, 76.54, 79.31, 80.80, 82.87 (C-1–5), and 206.38 (C-2′).

Anal. Calc. for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.45; H, 8.50.

The conditions used for other *C*-ribofuranosylation reactions are shown in Table I. In the cases of reactions involving **5, 7,** and **8**, the work-up after the reaction was different; the combined filtrate and washings were separated in a separatory funnel instead of being evaporated, and the extraction was performed with

dichloromethane. The aqueous layer was further extracted 5 times with dichloromethane.

1-(2,3-Di-O-benzyl-5-O-methyl-α-D-ribofuranosyl)-2-propanone (**22α**). — Syrup, $[\alpha]_D^{22}$ +35.7° (*c* 0.98, chloroform); ν_{max}^{NaCl} 1715 (C=O) cm^{-1}; ^{1}H-n.m.r. (200 MHz): δ 2.05 (s, 3 H, H-3′), 2.80 (dd, 1 H, $J_{1,1'}$ 6.1, $J_{1',1''}$ 17.1 Hz, H-1′), 2.93 (dd, 1 H, $J_{1,1''}$ 7.6 Hz, H-1″), 3.32 (s, 3 H, OCH_3), 3.37 (dd, 1 H, $J_{4,5}$ 4.6, $J_{5,5'}$ 10.5 Hz, H-5), 3.47 (dd, 1 H, $J_{4,5'}$ 3.2 Hz, H-5′), 3.96–4.14 (m, 3 H, H-2,3,4), 4.44, 4.78 (2 H, AB type, *J* 11.3 Hz, CH_2Ph), 4.55, 4.68 (2 H, AB type, *J* 11.8 Hz, CH_2Ph), 4.35–4.55 (m, 1 H, H-1), and 7.25–7.34 (bd, 10 H, 2 C_6H_5); ^{13}C-n.m.r.: δ 30.63 (C-3′), 43.90 (C-1′), 59.24 (OCH_3), 72.69, 73.54, 76.02, 77.65, 79.05, 79.69 (C-1–5 and 2 CH_2Ph), 127.56, 127.71, 127.94, 128.20, 128.32, 137.77, 138.15 (2 C_6H_5), and 207.23 (C-2′).

Anal. Calc. for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.65; H, 7.55.

1-(5-O-Benzyl-2,3-di-O-methyl-α-D-ribofuranosyl)-2-propanone (**24α**). — Syrup, $[\alpha]_D^{22}$ +5.3° (*c* 1.51, chloroform); ν_{max}^{NaCl} 1705 (C=O) cm^{-1}; ^{1}H-n.m.r. (200 MHz): δ 2.17 (s, 3 H, H-3′), 2.76 (dd, 1 H, $J_{1,1'}$ 6.8, $J_{1',1''}$ 17.6 Hz, H-1′), 2.89 (dd, 1 H, $J_{1,1''}$ 6.8 Hz, H-1″), 3.41 (s, 3 H, OCH_3), 3.44 (s, 3 H, OCH_3), 3.52 (dd, 1 H, $J_{4,5}$ 4.0, $J_{5,5'}$ 11.0 Hz, H-5), 3.60 (dd, 1 H, $J_{4,5'}$ 3.7 Hz, H-5′), 3.82 (dd, 1 H, $J_{2,3}$ 4.6, $J_{3,4}$ 5.8 Hz, H-3), 3.92 (t, 1 H, $J_{1,2}$ 4.6 Hz, H-2), 4.05 (dt, 1 H, H-4), 4.49 (dt, 1 H, H-1), 4.51, 4.61 (2 H, AB type, *J* 12.5 Hz, CH_2Ph), and 7.24–7.44 (bs, 5 H, C_6H_5); ^{13}C-n.m.r. (50 MHz): δ 30.63 (C-3′), 43.70 (C-1′), 58.49, 59.60 (2 OCH_3), 70.36, 73.37, 75.81, 79.23, 79.55, 82.06 (C-1–5 and CH_2Ph), 127.45, 128.20, 138.06 (C_6H_5), and 207.02 (C-2′).

Anal. Calc. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.45; H, 7.76.

1-(5-O-Benzyl-2,3-di-O-methyl-β-D-ribofuranosyl)-2-propanone (**24β**). — Syrup, $[\alpha]_D^{22}$ −3.2° (*c* 0.95, chloroform), ν_{max}^{NaCl} 1705 (C=O) cm^{-1}; ^{1}H-n.m.r. (200 MHz): δ 2.17 (s, 3 H, H-3′), 2.68 (d, 2 H, $J_{1,1'}$ 6.4 Hz, H-1′), 3.41 (s, 3 H, OCH_3), 3.46 (s, 3 H, OCH_3), 3.54 (d, 2 H, $J_{4,5}$ 4.0 Hz, H-5), 3.47–3.56 (1 H, overlapped with H-5,H-2), 3.78 (t, 1 H, $J_{2,3}$ 4.0, $J_{3,4}$ 4.0 Hz, H-3), 4.11 (q, 1 H, H-4), 4.32 (q, 1 H, $J_{1,2}$ 6.4 Hz, H-1), 4.56 (bs, 2 H, CH_2Ph), and 7.32 (s, 5 H, C_6H_5); ^{13}C-n.m.r. (50 MHz): δ 30.48 (C-3′), 47.72 (C-1′), 57.70, 57.93 (2 OCH_3), 70.33, 73.36, 76.46, 79.37, 80.95, 82.96 (C-1–5 and CH_2Ph), 127.39, 127.50, 128.23, 138.00 (C_6H_5), and 206.29 (C-2′).

Anal. Calc. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.16; H, 7.63.

3-(2,3,5-Tri-O-methyl-α-D-ribofuranosyl)-1-propene (**17**). — Syrup, $[\alpha]_D^{22}$ +49.2° (*c* 1.22, chloroform); ^{1}H-n.m.r. (200 MHz): δ 2.44 (t, 2 H, $J_{1,1'}$ 7.1, $J_{1',2'}$ 6.9 Hz, H-1′), 3.39 (s, 3 H, OCH_3), 3.45 (s, 3 H, OCH_3), 3.47 (dd, 1 H, $J_{4,5}$ 4.3, $J_{5,5'}$ 10.6 Hz, H-5), 3.53 (s, 3 H, OCH_3), 3.56 (dd, 1 H, $J_{4,5'}$ 3.1 Hz, H-5′), 3.78 (dd, 1 H, $J_{1,2}$ 4.0, $J_{2,3}$ 4.5 Hz, H-2), 3.81 (dd, 1 H, $J_{3,4}$ 6.5 Hz, H-3), 4.05 (2 H, overlapped dt and ddd, H-1 and -4, respectively), 5.06 (dd, 1 H, $J_{2',3'}$ 10.2, $J_{3',3''}$ 1.9 Hz, H-3′), 5.13 (dd, 1 H, $J_{2',3''}$ 17.1 Hz, H-3″), and 5.82 (ddt, 1 H, H-2′); ^{13}C-n.m.r. (50 MHz): δ 33.87 (C-1′), 58.40, 59.24, 59.71 (3 OCH_3), 72.90, 78.91, 79.55, 79.75, 82.03 (C-1–5), 116.62 (C-3′), and 134.68 (C-2′).

Anal. Calc. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 59.63; H, 9.06.

3-(2,3-Di-O-benzyl-5-O-methyl-α-D-ribofuranosyl)-1-propene (**18**). — Syrup, $[\alpha]_D^{21}$ +48.5° (*c* 1.18, chloroform); ^{1}H-n.m.r. (360 MHz): δ 2.51 (t, 2 H, $J_{1,1'}$ 7.0, $J_{1',2'}$ 6.9 Hz, H-1′), 3.33 (s, 3 H, OCH_3), 3.39 (dd, 1 H, $J_{4,5}$ 4.2, $J_{5,5'}$ 10.7 Hz, H-5), 3.54 (dd, 1 H, $J_{4,5'}$ 2.9 Hz, H-5′), 3.97 (t, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 4.3 Hz, H-3), 4.05 (2 H, completely overlapped dt and dd, H-1 and -3, respectively), 4.17 (ddd, 1 H, $J_{3,4}$ 7.3 Hz, H-4), 4.53, 4.67 (2 H , AB type, *J* 12 Hz, CH_2Ph), 4.59, 4.82 (2 H, AB type, *J* 11.5 Hz, CH_2Ph), 5.03 (bd, 1 H, $J_{2',3'}$ 10.2 Hz, H-3′), 5.09 (bd, 1 H, $J_{2',3''}$ 17.2 Hz, H-3″), 5.78 (ddt, 1 H, H-2′), and 7.22–7.35 (bs, 10 H, 2 C_6H_5); ^{13}C-n.m.r. (50 MHz): δ 34.16 (C-1′), 59.22 (OCH_3), 72.49, 72.58, 73.25, 77.51, 79.05, 79.81, 79.99 (C-1–5 and CH_2Ph), 116.68 (C-3′), 127.42, 127.53, 127.59, 128.15, 128.26, 137.86, 138.33 (2 C_6H_5), and 134.80 (C-2′).

Anal. Calc. for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 75.21; H, 7.55.

3-(5-O-Benzyl-2,3-di-O-methyl-α-D-ribofuranosyl)-1-propene (**19**). — Syrup, $[\alpha]_D^{22}$ +34.2° (*c* 1.52, chloroform); ^{1}H-n.m.r. (200 MHz): δ 2.44 (t, 2 H, $J_{1,1'}$ 7.1, $J_{1',2'}$ 7.1 Hz, H-1′), 3.40 (s, 3 H, OCH_3), 3.52 (s, 3 H, OCH_3), 3.54 (dd, 1 H, $J_{4,5}$ 4.2, $J_{5,5'}$ 10.5 Hz, H-5), 3.64 (dd, 1 H, $J_{4,5'}$ 3.4 Hz, H-5′), 3.77 (t, 1 H, $J_{1,2}$ 4.3, $J_{2,3}$ 4.4 Hz, H-2), 3.86 (dd, 1 H, $J_{3,4}$ 6.6 Hz, H-3), 4.06 (dt, 1 H, H-1), 4.08 (dt, 1 H, H-4), 4.53, 4.63 (2 H, AB type, *J* 12.2 Hz, CH_2Ph), 5.06 (bd, 1 H, $J_{2',3'}$ 10.4 Hz, H-3′), 5.13 (bd, 1 H, $J_{2',3''}$ 17.0 Hz, H-3″), 5.83 (ddt, 1 H, H-2′), and 7.26–7.33 (bs, 5 H, C_6H_5); ^{13}C-n.m.r. (50 MHz): δ 35.92 (C-1′), 60.40, 61.68 (2 OCH_3), 72.33, 75.609, 81.23, 82.78, 81.84, 84.143 (C-1–5 and CH_2Ph), 118.60 (C-3′), 129.39, 130.14, 140.15 (C_6H_5), and 136.80 (C-2′).

Anal. Calc. for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 70.00; H, 8.25.

2-(2,3,5-Tri-O-benzyl-D-ribofuranosyl)-3-pentanone (**13**), *2-(2,3,5-tri-O-methyl-D-ribofuranosyl)-3-pentanone* (**21**), *and 2-(2,3-di-O-benzyl-5-O-methyl-D-ribofuranosyl)-3-pentanone* (**23**). — Repeated chromatography on a column of silica gel afforded only a trace amount (5–10 mg) of each pure compound. It was not possible to establish the configuration of these compounds.

Compound **13**. Syrup, ν_{max}^{NaCl} 1720 (C=O) cm^{-1}; ^{1}H-n.m.r. (360 MHz): δ 0.76 (t, 3 H, $J_{3',4'}$ 7.2, $J_{3'',4'}$ 7.2 Hz, H-4′), 1.09 (d, 3 H, $J_{1',1''}$ 7.1 Hz, H-1″), 2.14 (dq, 1 H, $J_{3',3''}$ 18.4 Hz, H-3′), 2.35 (dq, 1 H, H-3″), 2.99 (dq, 1 H, $J_{1,1'}$ 9.2 Hz, H-1′), 3.44 (dd, 1 H, $J_{4,5}$ 4.2, $J_{5,5'}$ 10.7 Hz, H-5), 3.53 (dd, 1 H, $J_{4,5'}$ 3.3 Hz, H-5′), 3.93 (dd, 1 H, $J_{2,3}$ 5.0, $J_{3,4}$ 5.0 Hz, H-3), 4.03 (dd, 1 H, $J_{1,2}$ 4.8 Hz, H-2), 4.05 (ddd, 1 H, H-4), 4.19 (dd, 1 H, H-1), 4.22, 4.41–4.67 (1 H and 5 H, 3 AB type, 3 CH_2Ph), and 7.18–7.26 (m, 15 H, 3 C_6H_5).

Anal. Calc. for $C_{31}H_{36}O_5$: C, 76.20; H, 7.43. Found: C, 75.91; H, 7.47.

Compound **21**. Syrup, ν_{max}^{NaCl} 1735 (C=O) cm^{-1}; ^{1}H-n.m.r. (360 MHz): δ 1.01 (t, 3 H, $J_{3',4'}$ 7.3 Hz, H-4′), 1.18 (d, 3 H, $J_{1',1''}$ 7.1 Hz, H-1″), 2.55 (q, 2 H, H-3′), 2.98 (dq, 1 H, $J_{1,1'}$ 9.6 Hz, H-1′), 3.32, 3.37, 3.43 (s, 3 × 3 H, 3 OCH_3), 3.44 (dd, 1 H, $J_{4,5}$ 4.3, $J_{5,5'}$ 10.7 Hz, H-5), 3.54 (dd, 1 H, $J_{4,5'}$ 3.0 Hz, H-5′), 3.69 (dd, 1 H, $J_{2,3}$ 4.8, $J_{3,4}$ 7.2 Hz, H-3), 3.80 (t, 1 H, $J_{1,2}$ 4.8 Hz, H-2), 3.90 (ddd, 1 H, H-4), and 4.18 (dd, 1 H, H-1).

Anal. Calc. for $C_{13}H_{24}O_5$: C, 59.98; H, 9.29. Found: C, 60.03; H, 9.07.

Compound **23**. Syrup, ν_{max}^{NaCl} 1725 (C=O) cm^{-1}; ^{1}H-n.m.r. (360 MHz): δ 0.83 (t, 3 H, $J_{3',4'}$ 7.2, $J_{3'',4'}$ 7.2 Hz, H-4′), 1.10 (d, 3 H, $J_{1',1''}$ 9.8 Hz, H-1″), 2.21 (dd, 1 H, $J_{3',3''}$ 18.3 Hz, H-3′), 2.41 (dd, 1 H, H-3″), 3.05 (dq, 1 H, $J_{1,1'}$ 9.8 Hz, H-1′), 3.34 (s, 3 H, OCH_3), 3.40 (dd, 1 H, $J_{4,5}$ 4.5, $J_{5,5'}$ 10.6 Hz, H-5), 3.53 (dd, 1 H, $J_{4,5'}$ 3.1 Hz, H-5′), 3.96 (dd, 1 H, $J_{2,3}$ 4.6, $J_{3,4}$ 4.7 Hz, H-3), 4.09 (ddd, 1 H, H-4), 4.10 (t, 1 H, $J_{1,2}$ 4.6 Hz, H-2), 4.25 (dd, 1 H, H-1), 4.28, 4.75 (2 H, AB type, J 11.6 Hz, CH_2Ph), 4.58, 4.70 (2 H, AB type, J 12 Hz, CH_2Ph), and 7.26–7.35 (m, 10 H, 2 C_6H_5).

Anal. Calc. for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.25; H, 7.57 (susceptible to decomposition).

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NEW APPROACHES TO SYNTHETIC RECEPTORS. STUDIES ON THE SYNTHESIS AND PROPERTIES OF MACROCYCLIC *C*-GLYCOSYL COMPOUNDS AS CHIRAL, WATER-SOLUBLE CYCLOPHANES*

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ABSTRACT

In an approach for the preparation of macrocyclic *C*-glycosyl compounds, the *C*-glycosyl residue is synthesized by acid-assisted reduction of a cyclic hemiacetal with sodium cyanoborohydride. Macrocycle formation is effected by the reaction of a symmetrical bis(*C*-glycosyl)derived diamine with a dicarboxylic acid dichloride. The product macrocycles are presented as the first examples of a new type of chiral, water-soluble cyclophane. Molecules of this type are of interest as synthetic receptors for lipophilic substrates.

INTRODUCTION

The design and preparation of model receptor–substrate systems, complementary pairs of water-soluble organic molecules, which will form stable bimolecular complexes, is an interesting contemporary challenge for synthetic organic chemists. The importance of intermolecular interactions between organic molecules and the need to understand the forces which govern such binding interactions are widely recognized. Current treatises on molecular biology and biochemistry are replete with examples of bimolecular complex-formation involving organic molecules. Ongoing efforts in many laboratories are directed toward molecular-level descriptions of how changes in drug structure lead to changes in drug–receptor interactions and response. Model receptor–substrate systems will allow detailed analyses of the solvent effects and intermolecular forces which control molecular interactions in aqueous solutions.

Our goal is to develop new synthetic approaches for preparing chiral, water-soluble molecules which have hydrophobic cavities. Such synthetic receptors (mol. wt., 650–1500) will support a rational approach to understanding the details of organic-molecular interactions in aqueous solution. These molecules are designed to form molecular complexes with benzenoid or other lipophilic substrates. The

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complexes (inclusion compounds) will be stabilized by van der Waals and solvent liberation (hydrophobic) forces, and therefore different from and complementary to the much more extensively studied crown-ether type "receptor"[1-4]. In this paper, we demonstrate that *C*-glycosyl residues may be used as structural units for the preparation of water-soluble macrocycles. The potential advantages of this approach to synthetic receptors will be described, and the preparation of two macrocyclic *C*-glycosyl derivatives will be detailed.

Designs for water-soluble macrocylic receptors. — Important observations relevant to the design of water-soluble, hydrophobic binding sites for small organic molecules have been recorded over the past 10 years[5-14]. Our approach to synthetic water-soluble receptors is founded upon these creative early investigations.

This project was begun to test the possibility that *C*-glycosyl compounds may be useful for the preparation of synthetic receptors. The essential feature of the early approaches to synthetic receptors (Fig. 1a) was the combination of the cyclophane (which defined the lipophilic cavity) with ionic groups (which rendered the cavity water-soluble). The idea presented here (Fig. 1b) is that aldose-derived structural units may be incorporated into a lipophilic macrocyclic ring. It is hypothesized that the resulting macrocyclic products will function as synthetic receptors analogous to Koga's molecules if (a) the macrocycle is water soluble (mM solutions would be adequate) and (b) the macrocycle encloses a lipophilic pocket.

This idea is a logical extension of the earlier work and has some interesting features. First, the approach allows the preparation of *chiral* receptors of known absolute configuration. No chiral and enantiomerically pure macrocyclic, water-soluble cyclophane has been reported to bind lipophilic substrates in aqueous

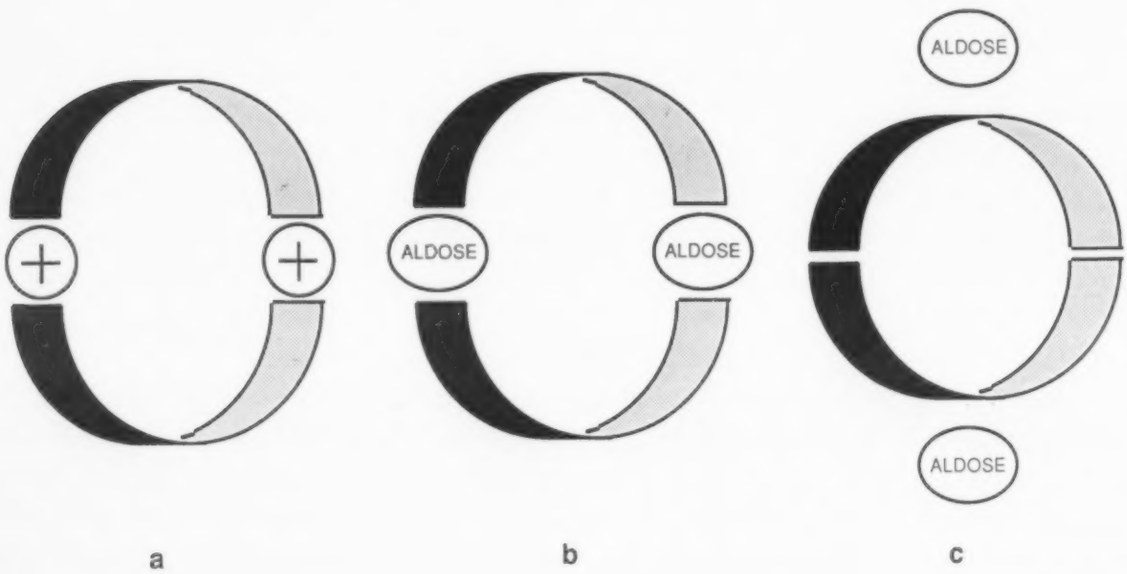
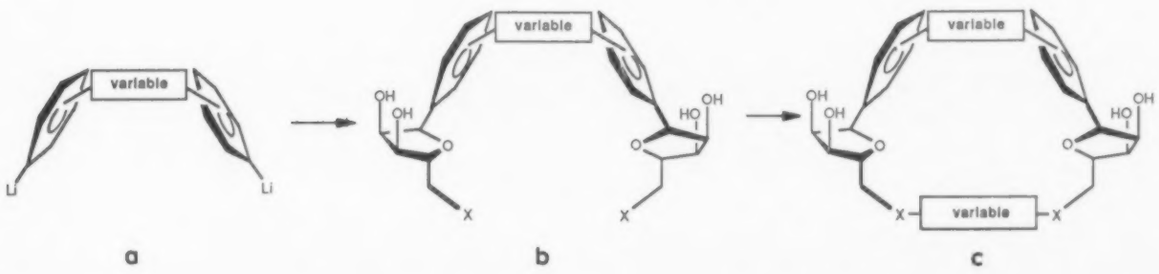


Fig. 1. Lipophilic macrocyclic binding sites may be rendered water soluble by the use of ionic functional groups (a), or by including aldose-derived polyhydroxylated substructures within the ring (b), or exterior to the ring (c).

solution. Because the chiral units are contained within the ring (rather than exterior to the ring, as shown in Fig. 1c) the receptors will provide substantially *chiral interior environments.* Such chiral cavities may allow the creation of enantioselective synthetic receptors which would be effective in aqueous media. Second, the strategy will allow the prepration of *neutral,* water-soluble cyclophanes. Neutral synthetic receptors will allow the effects of ionic charge on intermolecular forces to be systematically assessed. Finally, the hydroxyl groups carried by the aldose units will provide additional attractive interactions with some substrates, will be reactive toward other substrates, and can be used to attach additional functional groups. These functionalized synthetic receptors should be promising armatures for the construction of biomimetic systems.

The synthetic approach. — The target molecules in this project (Fig. 1b) represent a "second generation" approach to water-soluble binding sites for lipophilic substrates. Syntheses of these molecules should be short and efficient. We sought a protocol which would be modular and incorporate structural units that could be easily varied. If successful, such a strategy would allow the preparation of a number of related synthetic receptors.

The general strategy (Scheme 1) takes appropriate advantage of the fact that the targets have at least one C_2 axis of symmetry. It was envisioned that a symmetrically lithiated aryl compound (**a**) be stereospecifically ribosylated to afford a chiral bis(*C*-glycosyl) derivative (**b**) of C_2 symmetry. Model studies indicated that *C*-D-ribofuranosyl glycosides of α configuration would be suitable for preparing macrocycles which would include a lipophilic cavity. The intermediate **b** may be converted into the desired macrocyclic target **c** by any of a number of methods. For example, as shown below, macrocyclization may be effected by the reaction of a chiral diamine, derived from this bis(*C*-glycosyl) compound, with a dicarboxylic acid dichloride. The construction of the macrocycle is substantially simplified because the synthesis proceeds symmetrically outward from the axis of symmetry. The choice of the dilithio unit (**a**) and the means of cyclization (the two variable units in Scheme 1) will affect the properties of the ultimate macrocycle. A *C*-glycosyl linkage was chosen for attaching the lipophilic unit to the aldose residue because the carbon–carbon bond in the *C*-glycosyl compound will be more robust



Scheme 1. A generalized approach for preparing macrocyclic *C*-glycosyl compounds.

(less reactive) than the carbon–oxygen bond in glycosides, and the direct connection of an aryl group to C-1 of the aldosyl residue provides a more rigid structure than would result from a glycosidic linkage. The D-ribofuranose unit was chosen because it is readily available in a protected form from D-ribonic acid and because the 2,3-*O*-isopropylidene protecting group offered the possibility of controlling the stereochemical outcome of the *C*-glycosylation process.

RESULTS AND DISCUSSION

The approach outlined in Scheme 1 required a stereoselective method for forming α-D-ribofuranosylarenes. Previous work in this area indicated that nucleophilic additions of alkylmetals to activated D-ribofuranose derivatives affords mixtures of anomeric products[15]. Based on experience in a related system, we hypothesized that hydride donation to a cationic intermediate would lead more cleanly to the desired *C*-α-D-glycosyl compounds.

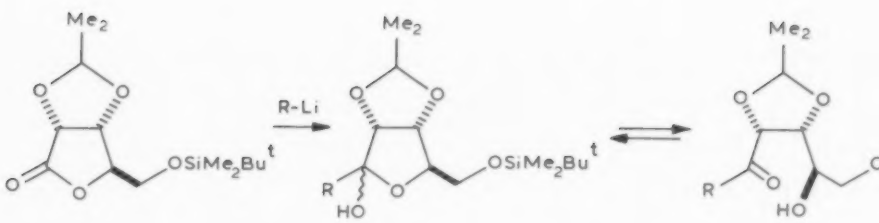
To test this possibility, the D-ribonolactone derivative **1** was alkylated to afford hemiacetals **2–8**. The product hemiacetals were obtained in excellent yield (Table I) as mixtures of anomeric isomers. In contrast to the other adducts, the 4-(dimethylamino)phenyl derivative **8** exists (in $CDCl_3$ or CCl_4 solution) only in the keto-hydroxy form (**8b**) and no hemiacetal was observable by ^1H- or ^{13}C-n.m.r. spectroscopy. Under similar conditions, the other products **2–7** were preponderantly in the hemiacetal form (**2a–7a**). The stability of the open form of **2g** probably

TABLE I

FORMATION AND REDUCTION OF THE CYCLIC HEMIACETALS **2–8**

Starting compound	*Hemiacetal formed*		*Reduction*				
	Residue at C-1	*Yield (%)*[a]	*Conditions*[b]	*C-Glycosyl compounds formed*			
				Compound	*Yield (%)*	*Compound*	*Yield (%)*
2	Me	97	A	**10**	0	**17**	0
			B		0		0
3	Ph	94	A	**11**	0	**18**	0
			B		68		0
4	4-(Me)C_6H_4	100	B	**12**	63	**19**	19
5	4-(MeO)C_6H_4	100	A	**13**	98	**20**	0
6	4-Biphenyl	96	B	**14**	66	**21**	17
7	2-Furyl	96	A	**15**	62	**22**	0
			B		73		24
8	4-(Me_2N)C_6H_4	31	B	**16**	0	**23**	0

[a]All yields reported for isolated products. [b]Conditions: (A) *p*-toluenesulfonic acid–methanol, room temp.; (B) dichloroacetic acid–2,2,2-trifluorethanol, room temp. See Experimental section.



$SiMe_2Bu^t$ = (1,1-dimethylethyl)dimethylsilyl

2, 10, 17 R = Me
3, 11, 18 R = Ph
4, 12, 19 R = 4-MeC_6H_4
5, 13, 20 R = 4-$MeOC_6H_4$
6, 14, 21 R = 4-Biphenyl
7, 15, 22 R = 2-Furyl
8, 16, 23 R = 4-$(Me_2N)C_6H_4$

contributes to the low yield observed for its formation. The major by-product was the diol formed by reaction of a second alkyllithium reagent.

Reduction of carbohydrate-derived acetals has been studied for many years and has been achieved most recently by the use of triethylsilane with Lewis acid catalysts[16,17]. In this case, the goal was a direct reduction of the hemiacetal and we chose to evaluate sodium cyanoborohydride for this purpose because it is readily available and inexpensive.

The direct reduction of hemiacetals to afford *C*-glycosyl compounds (**10–16** and **17–23**) proceeded in good to excellent yield (Table I), provided that the alkyl group at C-1 was adequately electron releasing. A limited study of solvent and proton source indicated that nitromethane or 2,2,2-trifluoroethanol are good solvents for this reaction and dichloroacetic acid is an adequate proton source. The products had preponderantly the α-D configuration and in two cases the α-D anomer was the only cyclic product obtained. The product structures could be readily determined by established spectroscopic methods including ^{13}C- and ^{1}H-n.m.r. spectroscopy[18–21].

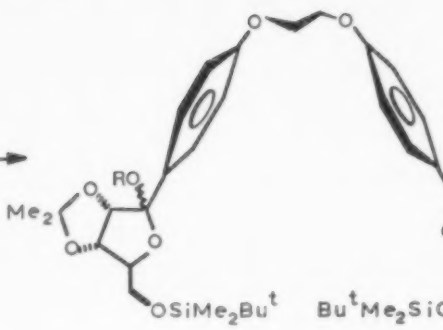
The process just outlined afforded a completely stereoselective method for preparing (4-alkoxy)aryl derivatives of (4-alkoxyl)-α-D-ribofuranosylarenes and attention was therefore turned toward preparation of the requisite macrocyclic *C*-glycosyl compounds.

Bromination of diphenoxyethane afforded the 4,4′-dibromo derivatives **25** in 86% yield[22]. Alkylation of dilithium compound **26** in oxolane with the lactone **1** under the conditions applied in the model systems provided the bis(hemiacetals) **27**. Reduction of the bis(hemiacetal) **27** proceeded as expected based upon the model studies and provided a quantitative yield of the desired bis(*C*-glycosyl) compound **29**. The only product detected by ^{1}H- or ^{13}C-n.m.r. spectroscopy was the desired α-D anomer. After removal of the protecting group at O-5′ and chromatographic purification, the diol **30** was obtained (80% overall yield from lactone **1**). This symmetrical diol (**30**) was converted into the diamine **32** *via* the Mitsunobu–Gabriel procedure[23]. This diamine, with terephthaloyl chloride, under the high dilution conditions described by Dietrich *et al.*[24] provided the *C*-glycosyl macrocycle **34** (*m/e* calc. 686.2839; found 686.2823) in 15% yield after purification. Deprotection of this macrocycle afforded the desired tetrahydroxy macrocyclic diamide **35** in good yield. In a similar manner, diamine **32** and the dicarboxylic acid dichloride derived from 2,3-*O*-methylene-D-tartaric acid[25] afforded the macrocyclic diamide **33** in 10% overall yield.

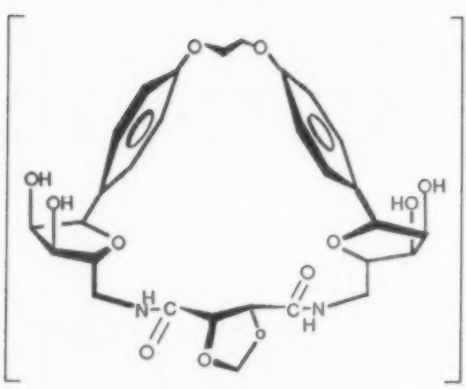
CONCLUSION

Inevitably, water-soluble synthetic receptors more complex than the simple cyclophanes currently known must be synthesized. The results described herein establish a general approach for preparing *C*-glycosyl macrocycles of a type previously unknown. By this approach, for the first time, a cyclophane-like molecule has been rendered water soluble without the use of ionic groups.

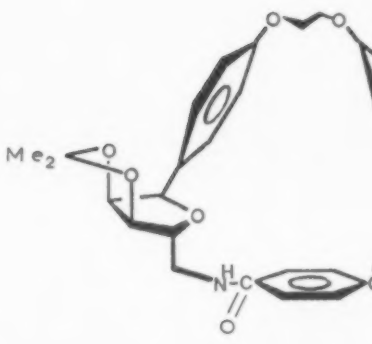
25 R = Br
26 R = Li



27 R = H
28 R = Me

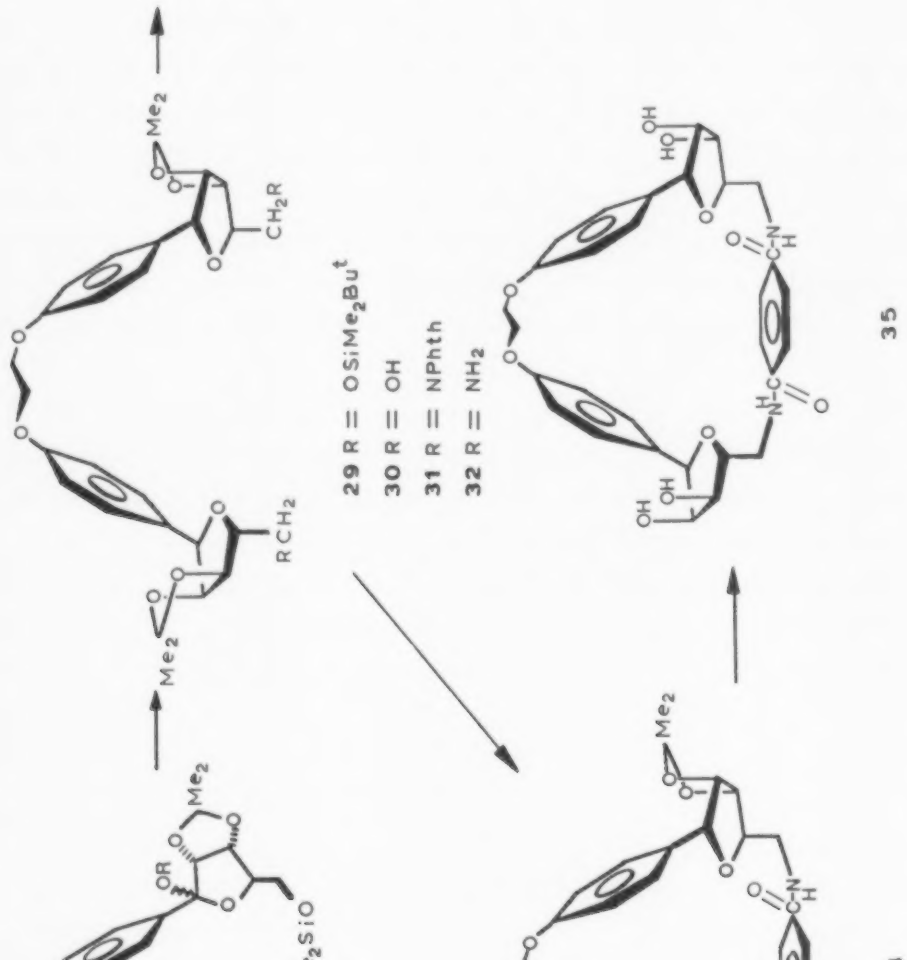


33



34

$SiMe_2Bu^t$ = (1,1-dimethylethyl)dimethylsilyl


29 R = OSiMe2But
30 R = OH
31 R = NPhth
32 R = NH2
35

For convenient n.m.r. studies of binding properties, it is necessary that monomeric synthetic receptor solutions of at least mM concentration be attainable. We found that aqueous solutions of the tartaric acid diamide macrocycle (**33**) were readily prepared. N.m.r. spectra of these solutions in D_2O showed no changes over the concentration range from 0.5 to 50mM. In contrast, the terephthalamide macrocycle (**35**) has very low solubility. Sonication of warm solutions of **35** in deuterium oxide, followed by centrifugation, provided a supernatant centrifugate which gave no usable n.m.r. signal. The limiting solubility of **35** is therefore probably below 0.5mM.

We conclude that this approach to water-soluble macrocyles, prototypes for a new generation of synthetic receptors for small organic molecules, is promising and worthy of further exploration. A more rigid dilithium unit will afford a less flexible diamine intermediate and should lead to improved yields in the macrocyclization step. Further control of conformation and additional enhancement of solubility will be obtainable by prudent selection of the dicarboxylic acid dichloride component of the cyclization reaction.

EXPERIMENTAL

General methods. — Melting points were determined with a Thomas–Hoover capillary melting-point apparatus and are uncorrected. Boiling points are uncorrected. Optical rotations were measured in 1-dm cells of 1-mL capacity with a Perkin–Elmer Model 141 polarimeter. Chloroform was used as the solvent for all optical rotations and was filtered through neutral alumina immediately prior to use. ^{1}H-N.m.r. spectra were recorded with Varian EM-390, Nicolet NT-200, and Nicolet NMC-1280 spectrometers. Chemical shifts (δ) are reported relative to the signal of tetramethylsilane (δ 0.0) as an internal standard. ^{13}C-N.m.r. spectra were recorded with Varian FT80 and Nicolet NMC-1280 spectrometers. Chemical shifts (δ) are reported relative to the signal of tetramethylsilane (δ 0.0) as an internal standard, or relative to that of $CDCl_3$ (δ 77.0). I.r. spectra were determined with a Perkin–Elmer 298 spectrometer for solutions in carbon tetrachlorideunless oherwise stated. Low-resolution mass spectra were obtained with Finnigan GC/MS and Dupont (CEC) 21-491 spectrometers, and high-resolution mass spectra with a Dupont (CEC) 21-11 spectrometer. T.l.c. was conducted on 2.5 × 10 cm pre-coated t.l.c. plates, Silica gel 60 F-254, layer thickness 0.25 mm, manufactured by E. Merck and Co., Darmstadt, Germany. Flash column chromatography was carried out on Silica gel 60 (E. Merck, particle size 0.040–0.063 mm, 230–400 mesh ASTM). "Dry" solvents were distilled shortly before use from the appropriate drying agent. Ether and oxolane were distilled under dry N_2 from Na metal in the presence of benzophenone. Methanol and pentane were distilled from Na metal under dry N_2. Benzene, dichloromethane, pyridine, and 1,2-dimethoxyethane were distilled from CaH_2. *N,N*-Dimethylformamide was distilled from CaH_2 at 74° and 7.2 KPa (54 mm Hg). Other reagents were purified as follows. Dimethyl sulfoxide was

fractionally distilled from CaH_2 at 50° and 0.5 KPa (4 mm Hg), and triethylamine from Na metal. 1-Chloro-2,2,3,3-tetramethyl-2-silapropane (*t*-butyldimethylsilyl chloride) was sublimed at 80° and 0.1 MPa (750 mm Hg). Ethyl acetate was stored over molecular sieves (4A, 4–8 mesh) at least 10 days prior to use. All other reagents and solvents were "Reagent Grade" unless described otherwise. "Ether" refers to anhydrous diethyl ether which is supplied by Matheson, Coleman, and Bell. "Petroleum ether" and "Skelly B" are used interchangeably to refer to reagent grade hexanes (b.p. 60–70°), purified by stirring for 24 h over conc. H_2SO_4, stirring subsequently over anhydrous $CaCO_3$ for 24 h, and then fractionally distilling. Reactions were run under an N_2 atmosphere with a mercury bubbler arranged so that the system could be alternately evacuated and filled with N_2 and kept under a positive pressure of N_2. The temperature of reactions run without external cooling or heating ("room temperature") was 25 ±5°. Syringes, needles, and reaction flasks were dried at least 12 h in an oven (110°) and cooled in a dessicator over anhydrous $CaSO_4$ prior to use. Removal of solvents "under reduced pressure" refers to rotary evaporation at ~40° and 3 KPa (23 mm Hg), followed by evacuation under high vacuum (13 Pa, 0.1 mm Hg) to constant weight.

*1-Deoxy-6-*O*-[(1,1-Dimethylethyl)dimethylsilyl]-3,4-*O*-(1-methylethylidene)-*D*-psicofuranose* (**2**). — To a stirred solution of 5-*O*-[1,1-dimethylethyl)dimethylsilyl]-2,3-*O*-(1-methylethylidene)-D-ribono-1,5-lactone (**1**; 906 mg, 3.00 mmol) in oxolane (10 mL) at −78° was added a 1.41M ethereal solution of methyllithium (2.13 mL, 3.00 mmol). After 6 h at −78°, methanol (1 mL) was added and the mixture allowed to warm to room temperature. The mixture was partitioned between ether (80 mL) and water (40 mL). The organic layer was separated, washed with water (40 mL), and dried ($MgSO_4$). Removal of solvent under reduced pressure and purification of the residue by flash chromatography (40 × 150 mm column of SiO_2, 20% ethyl acetate–petroleum ether) afforded **2** (922 mg, 97%), colorless white syrup, $[\alpha]_D^{23}$ −10° (*c* 1.5, chloroform), R_F 0.42 (SiO_2, 20% ethyl acetate–petroleum ether); $\nu_{max}^{CCl_4}$ 3550, 3500–3300, 3000, 2960, 2930, 2860, 1380, 1350, 1100, and 1050 cm^{-1}; ^{1}H-n.m.r. (CCl_4): δ 0.05 (s, 6 H), 0.90 (s, 9 H), 1.23 (s, 3 H), 1.33 (s, 3 H), 1.39 (s, 3 H), 3.60 (d, 2 H, *J* 5 Hz), 4.00 (m, 1 H), 4.28 (d, 1 H, *J* 5 Hz), and 4.68 (d, 1 H, *J* 5 Hz); ^{13}C-n.m.r. ($CDCl_3$): δ 18.06, 21.17, 25.02, 25.60, 26.47, 64.76, 81.95, 85.67, 87.74, 106.39, and 112.16; m.s. ($M^+ - CH_3$): Calc. for $C_{14}H_{27}O_5Si$, *m/z* 303.1618; found, 303.1628.

*5-*O*-[(1,1-Dimethylethyl)dimethylsilyl]-2,3-*O*-(1-methylethylidene)-1-*C*-phenyl-*D*-ribofuranose* (**3**). — By the procedure used to prepare **2**, **1** (906 mg) in oxolane (10 mL) and a 0.95M benzene–ether solution of phenyllithium (3.16 mL) afforded, after flash chromatography (40 × 150 mm column of SiO_2, 20% ethyl acetate–petroleum ether) afforded **3** (1.072 g, 94%), colorless white syrup (mixture of anomers), $[\alpha]_D^{23}$ −20° (*c* 1.5, ethanol), R_F 0.45 (SiO_2, 20% ethyl acetate–petroleum ether); $\nu_{max}^{CHCl_3}$ 3580, 2950, 2930, 2860, 1500, 1250, 1220, and 1080 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 0.02 (s, 6 H), 0.85 (s, 9 H), 1.06 (s, 3 H), 1.18 (s, 3 H), 3.63 (d, 2 H, *J* 6 Hz), 4.08 (m, 1 H), 4.36 (m, 1 H), 4.68 (d, 1 H, *J* 6 Hz), and 7.05–7.30

(m, 5 H); ^{13}C-n.m.r. ($CDCl_3$): δ 18.29, 24.87, 25.81, 26.39, 64.81, 81.97, 86.18, 88.65, 112.59, 125.69, 126.96, 127.42, 128.00, and 138.99; m.s. (M^+): Calc. for $C_{20}H_{32}O_5Si$, *m/z* 380.2014; found, 380.2019.

5-O-[(1,1-Dimethylethyl)dimethylsilyl]-2,3-O-(1-methylethylidene)-1-C-(4-methylphenyl)-D-ribofuranose (**4**). — To a stirred solution of 4-bromotoluene (1.026 g, 6.00 mmol) in oxolane at −78° was added a 1.8M solution of *tert*-butyllithium in pentane (7 mL, 12.2 mmol). The mixture was stirred at −78° for 1 h, allowed to warm to 0°, and then cooled to −78°. To this solution was added a solution of **1** (1.812 g, 6.00 mmol) in oxolane (15 mL). The mixture was stirred at −78° for 6 h, then methanol (1 mL) was added and the mixture allowed to warm to room temperature. The solution was poured into ether (200 mL) and washed twice with water (150 mL). The organic phase was dried ($MgSO_4$) and then evaporated under reduced pressure to give **4** (2.38 g, 100%), colorless white syrup, $[\alpha]_D^{23}$ −32° (*c* 1.5, chloroform), R_F 0.66 (SiO_2, 20% ethyl acetate–petroleum ether); $\nu_{max}^{CHCl_3}$ 3680, 3500–3200, 3000, 2960, 2940, 2860, 1520, 1470, 1420, 1380, 1370, 1220, and 1080 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 0.12 (s, 6 H), 0.93 (s, 9 H), 1.20 (s, 3 H), 1.38 (s, 3 H), 2.33 (s, 3 H), 3.70 (d, 2 H, *J* 3 Hz), 4.42 (s, 1 H), 4.58 (d, 1 H, 6 Hz), 4.89 (d, 1 H, *J* 6 Hz), 7.15 (d, 2 H, 8 Hz), and 7.51 (d, 2 H, *J* 8 Hz); ^{13}C-n.m.r. ($CDCl_3$): δ −5.83, 17.99, 20.88, 24.62, 25.59, 26.19, 64.51, 81.95, 85.84, 88.04, 106.74, 112.74, 126.74, 127.83, 136.13, and 137.07; m.s. (M^+): Calc. for $C_{21}H_{34}O_5Si$, *m/z* 394.2175; found, 394.2195.

5-O-[(1,1-Dimethylethyl)dimethylsilyl]-2,3-O-(1-methylethylidene)-1-C-(4-methoxyphenyl)-D-ribofuranose (**5**). — By the procedure used to prepare **4**, 4-bromoanisole (561 mg, 3.00 mmol) in oxolane (9 mL) with a 1.8M solution of *tert*-butyllithium in pentane (3.4 mL, 6.15 mmol) provided a solution of 4-lithio-1-methoxybenzene. This solution and **1** (906 mg, 3.00 mmol) in oxolane (9 mL) afforded **5** (1.230 g, 100%), colorless white syrup, $[\alpha]_D^{23}$ −45° (*c* 1.5, chloroform), R_F 0.39 (SiO_2, 20% ethyl acetate–petroleum ether); $\nu_{max}^{CCl_4}$ 3580, 3500–3200, 2960, 2940, 2860, 1685, 1600, 1510, 1380, 1370, 1250, and 1080 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 0.09 (s, 6 H), 0.90 (s, 9 H), 1.15 (s, 3 H), 1.28 (s, 3 H), 3.70 (m, 5 H), 4.18 (m, 1 H), 4.45 (d, 1 H, *J* 5 Hz), 4.75 (d, 1 H), 6.76 (d, 2 H, *J* 8 Hz), and 7.40 (d, 2 H, *J* 8 Hz); ^{13}C-n.m.r. ($CDCl_3$): δ 18.27, 25.55, 25.79, 26.42, 55.07, 64.79, 81.90, 86.02, 88.50, 106.80, 112.53, 112.83, 128.24, 131.24, and 159.35; m.s. ($M^+ - CH_3$): Calc. for $C_{20}H_{31}O_6Si$, *m/z* 395.1881; found, 395.1890.

1-C-[1,1'-Biphenyl]-4-yl-5-O-[(1,1-dimethylethyl)dimethylsilyl]-2,3-O-(1-methylethylidene)-D-ribofuranose (**6**). — By the procedure used to prepare **4**, 4-bromobiphenyl (671 mg, 3.00 mmol) in oxolane (9 mL) and a 1.8M solution of *tert*-butyllithium in pentane (3.4 mL, 6.15 mmol) provided a solution of 1-lithio-4-phenylbenzene. This solution and **1** (906 mg, 3.00 mmol) in oxolane (9 mL) afforded **6** (1.314 g, 96%), a colorless white syrup, $[\alpha]_D^{23}$ −54° (*c* 1.5, chloroform); R_F 0.52 (SiO_2, 20% ethyl acetate–petroleum ether); $\nu_{max}^{CHCl_3}$ 3680, 3400–3200, 3000, 2960, 2940, 2860, 1385, 1375, 1220, and 1080 cm^{-1}; ^{1}H-n.m.r. (CCl_4): δ 0.03 (s, 6 H), 0.90 (s, 9 H), 1.18 (s, 3 H), 1.30 (s, 3 H), 3.70 (d, 2 H, *J* 5 Hz), 4.12 (t, 1 H, *J*

5 Hz), 4.77 (m, 1 H), 5.05 (d, 1 H, *J* 4 Hz), and 7.35 (m, 9 H); ^{13}C-n.m.r. ($CDCl_3$): δ −5.65, 18.32, 24.59, 25.88, 26.54, 64.87, 82.13, 86.13, 88.68, 106.97, 112.71, 126.25, 126.82, 127.16, 127.53, 128.63, 138.25, 140.84, and 141.16; m.s. ($M^+ - CH_3 - H_2O$): Calc. for $C_{25}H_{31}O_5Si$, *m/z* 439.1994; found, 439.1940.

*5-O-[(1,1-Dimethylethyl)dimethylsilyl]-1-C-(2-furanyl)-2,3-O-(1-methylethylidene)-*D*-ribofuranose* (**7**). — To a stirred solution of furan (309 mg, 4.5 mmol) and tetramethylethylenediamine (105 mg, 0.9 mmol) in ether (3 mL) at −20° was added butyllithium in hexane (1.90 mL, 3.00 mmol). The mixture was allowed to warm to room temperature, and after 3 h stirring the mixture was cooled to −78° and oxolane (4 mL) was added to give a clear solution of 2-lithiofuran. A solution of **1** (906 mg, 3.00 mmol) in oxolane (10 mL) was added, and after stirring for 6 h at −78° methanol (1 mL) was added. The mixture was allowed to warm to room temperature, poured into ether (250 mL), and washed twice with M ammonium chloride (50 mL) and twice with saturated $NaHCO_3$ (50 mL). The organic phase was dried ($MgSO_4$) and then evaporated under reduced pressure to give a colorless white syrup. This was purified by flash chromatography (60 × 180 mm column of SiO_2, 20% ethyl acetate–petroleum ether) to give **7** (996 mg, 96%) as a colorless white syrup; it was present as three interconverting forms, two hemiacetal anomers and the open-chain ketonic form; therefore in the ^{13}C-n.m.r. spectrum only the major characteristic peaks are reported; $[\alpha]_D^{23}$ −44° (*c* 1.5, chloroform), R_F 0.35 (SiO_2, 18% ethyl acetate–petroleum ether); $\nu_{max}^{CCl_4}$ 3580, 3500–3250, 2960, 2940, 2850, 1700, 1475, 1390, 1380, 1260, 1220, and 1090 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 0.05 (s, 6 H), 0.90 (s, 9 H), 1.16, 1.29, 1.45, 1.50 (all s, total 6 H), 3.66 (d, 2 H, *J* 5 Hz), 4.18 (t, 1 H, *J* 5 Hz), 4.51, 4.70 (both, total 1 H), 5.23 (d, 1 H, *J* 5 Hz), 6.28 (m, 2 H), and 7.32 (m, 1 H); ^{13}C-n.m.r. ($CDCl_3$): δ 18.05, 24.67, 24.92, 25.31, 25.62, 26.07, 27.00, 64.46, 78.59, 81.95, 85.78, 88.30, 104.34, 108.04, 109.85, 112.62, 142.18, 151.40, and 184.00; m.s. ($M^+ - CH_3$): Calc. for $C_{17}H_{27}O_6Si$, *m/z* 355.1571; found, 355.1577.

*1-C-[4-(Dimethylamino)phenyl]-5-O-[(1,1-dimethylethyl)dimethylsilyl]-2,3-O-(1-methylethylidene)-*D*-ribofuranose* (**8**). — By the procedure used to prepare **4**, 4-bromo-*N,N*-dimethylaniline (600 mg, 3.00 mmol) in oxolane (9 mL) and a 1.8M solution of *tert*-butyllithium in pentane (3.4 mL, 6.15 mmol) provided a solution of 4-lithio-*N,N*-dimethylaniline. This solution and **1** (906 mg, 3.00 mmol) in oxolane (9 mL) afforded, after flash chromatography (40 × 150 mm column of SiO_2, 10% ethyl acetate–dichloromethane), **8** (31%), colorless white syrup, $[\alpha]_D^{23}$ +6.8° (*c* 1.5, chloroform), R_F 0.50 (SiO_2, 10% ethyl acetate–dichloromethane); $\nu_{max}^{CHCl_3}$ 3005, 2960, 2940, 2850, 1600, 1530, 1480, 1430, 1370, and 1220 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 0.05 (s, 6 H), 0.90 (s, 9 H), 1.33 (s, 3 H), 1.48 (s, 3 H), 2.89 (s, 3 H), 2.99 (s, 3 H), 3.79 (d, 2 H, *J* 3 Hz), 4.59 (m, 1 H), 4.70 (m, 1 H), 5.20 (d, 1 H, *J* 6 Hz), 6.65 (d, 2 H, *J* 10 Hz), and 8.80 (d, 2 H, 10 Hz); ^{13}C-n.m.r. ($CDCl_3$): δ 18.26, 25.83, 26.86, 27.23, 39.86, 64.03, 72.63; 76.69, 78.95, 110.53, 123.58, 131.79, 153.63, and 183.53; m.s. (M^+): Calc. for $C_{22}H_{37}O_5NSi$, *m/z* 423.2446; found, 423.2441.

(R)-1,4-Anhydro-5-O-[(1,1-dimethylethyl)dimethylsilyl]-2,3-O-(1-methylethylidene)-1-C-phenyl-D-ribitol (**11**). — To a stirred solution of **3** (692 mg, 1.82 mmol) in 2,2,2-trifluorethanol (14 mL) at room temperature was added first sodium cyanoborohydride (349 mg, 5.46 mmol), followed by dichloroacetic acid (705 mg, 5.46 mmol). The mixture was stirred at room temperature for 10 min, sat. aq. $NaHCO_3$ (10 mL) was added, and the mixture was poured into water (120 mL). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure to give a white oil. Chromatography (50 × 180 mm column of SiO_2, 15% ethyl acetate–petroleum ether) afforded **11** (448 mg, 68%), colorless white syrup, $[\alpha]_D^{23}$ −65° (*c* 1.5, chloroform), R_F 0.45 (SiO_2, 10% ethyl acetate–petroleum ether); ν_{max} 2980, 2960, 2930, 2860, 1600, 1495, 1440, 1420, 1410, 1260, 1210, and 1160 cm^{-1}; ^{1}H-n.m.r. (360 MHz, $CDCl_3$): δ 0.046 (s, 3 H), 0.894 (s, 9 H), 1.246 (s, 3 H), 1.397 (s, 3 H), 3.754 (dd, 1 H, *J* 10, *J* 3.6 Hz), 3.816 (dd, 1 H, *J* 10, *J* 3.6 Hz), 4.224 (t, 1 H, *J* 3.6 Hz), 4.776 (t, 1 H, *J* 5.4 Hz), 4.907 (d, 1 H, *J* 5.4 Hz), 5.194 (d, 1 H, *J* 4.7 Hz), and 7.18–7.38 (m, 5 H); ^{13}C-n.m.r. (90 MHz, $CDCl_3$): δ −5.59, 18.13, 24.79, 25.86, 26.16, 65.18, 83.23, 83.35, 84.30, 84.44, 112.37, 127.35, 127.53, 127.79, and 137.06; m.s. ($M^+ - CH_3$): Calc. for $C_{19}H_{29}O_4Si$, *m/z* 349.1835; found, 349.1841.

[R (**12**) *and* S]*-1,4-Anhydro-5-O-[(1,1-dimethylethyl)dimethylsilyl]-2,3-O-(1-methylethylidene)-1-C-(4-methylphenyl)-D-ribitol* (**19**). — By the procedure used to prepare **11**, **4** (624 mg, 1.584 mmol) in 2,2,2-trifluoroethanol (7 mL) at room temperature, sodium cyanoborohydride (200 mg, 4.752 mmol), and dichloroacetic acid (400 mg, 4.752 mmol) afforded, after chromatography (60 × 180 mm column of SiO_2, 10% ethyl acetate–petroleum ether), **12** and **18**.

Compound **12**. Yield 381 mg (63%), colorless white oil, $[\alpha]_D^{23}$ −85.5° (*c* 1.5, chloroform), R_F 0.51 (SiO_2, 10% ethyl acetate–petroleum ether); $\nu_{max}^{CHCl_3}$ 2960, 2930, 2860, 1615, 1470, 1460, 1380, 1370, 1255, 1210, 1130, and 1070 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 0.10 (s, 6 H), 0.90 (s, 9 H), 1.34 (s, 3 H), 1.50 (s, 3 H), 2.38 (s, 3 H), 3.87 (d, 2 H, *J* 3 Hz), 4.32 (t, 1 H, *J* 3 Hz), 4.85 (m, 1 H), 5.04 (m, 1 H), 5.28 (d, 1 H, *J* 5 Hz), and 7.22 (d, 2 H, *J* 7.5 Hz); ^{13}C-n.m.r. ($CDCl_3$): δ 18.08, 21.10, 24.70, 25.80, 26.41, 65.16, 83.31, 84.21, 84.35, 112.31, 127.34, 128.57, 133.90, and 137.16; m.s. (M^+): Calc. for $C_{21}H_{34}O_4Si$, *m/z* 378.2226; found, 378.2238.

Compound **19**. Yield 112 mg (19%), colorless white syrup, $[\alpha]_D^{23}$ −41° (*c* 1.5, chloroform), R_F 0.59 (SiO_2, 10% ethyl acetate–petroleum ether); $\nu_{max}^{CHCl_3}$ 2990, 2980, 2860, 2730, 1515, 1470, 1380, 1370, 1260, 1210, and 1080 cm^{-1}; ^{1}H-n.m.r. (360 MHz, $CDCl_3$): δ 0.115 (s, 3 H), 0.125 (s, 3 H), 0.943 (s, 9 H), 1.382 (s, 3 H), 1.647 (s, 3 H), 2.364 (s, 3 H), 3.878 (m, 2 H), 4.180 (dd, 1 H, *J* 7.2, *J* 3.6 Hz), 4.506 (dd, 1 H, *J* 6.8, *J* 5.4 Hz), 4.769 (dd, 1 H, 6.8 Hz, 3.6 Hz), 4.895 (d, 1 H, *J* 5.4 Hz), 7.170 (d, 2 H, *J* 8 Hz), and 7.326 (d, 2 H, *J* 8 Hz); ^{13}C-n.m.r. (90 MHz, $CDCl_3$): δ −5.42, 18.35, 21.07, 25.65, 25.90, 27.68, 63.42, 87.77, 84.54, 85.75, 82.25, 114.30, 125.76, 128.99, and 137.27; m.s. ($M^+ - CH_3$): Calc. for $C_{20}H_{31}O_4Si$, *m/z* 363.1992; found, 363.2009.

(R)-1,4-Anhydro-5-O-[(1,1-dimethylethyl)dimethylsilyl]-2,3-O-(1-methyl-

ethylidene)-1-C-*(4-methoxyphenyl)*-D-*ribitol* (**13**). — To a stirred solution of **5** (511 mg, 1.25 mmol) in methanol (8 mL) at room temperature was added first 4-toluenesulfonic acid monohydrate (400 mg, 2.10 mmol), and then sodium cyanoborohydride (233 mg, 3.75 mmol). After stirring for 5 min at room temperature, no starting material was detectable (t.l.c.). Sat. aq. $NaHCO_3$ (6 mL) was added, and the mixture was poured into ether (200 mL) and washed with sat. aq. $NaHCO_3$ (50 mL), and then water (20 mL). The organic layer was dried ($MgSO_4$) and then evaporated under reduced pressure to give **12** (479 mg, 98%), colorless white oil, $[\alpha]_D^{23}$ −32° (*c* 1.5, chloroform), R_F 0.39 (SiO_2, 10% ethyl acetate–petroleum ether); $\nu_{max}^{CHCl_3}$ 3010, 2960, 2940, 2860, 1515, 1425, 1385, 1375, and 1220 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 0.12 (s, 6 H), 0.93 (s, 9 H), 1.20 (s, 9 H), 1.38 (s, 3 H), 2.33 (s, 3 H), 3.70 (d, 2 H, *J* 3 Hz), 4.42 (s, 1 H), 4.58 (d, 1 H, *J* 6 Hz), 4.89 (d, 1 H, *J* 6 Hz), 7.15 (d, 2 H, *J* 8 Hz), and 7.51 (d, 2 H, *J* 8 Hz); ^{13}C-n.m.r. ($CDCl_3$): δ 18.3, 25.55, 25.8, 26.4, 55.1, 64.8 81.9, 86.0, 88.5, 106.8, 112.5, 112.8, 128.2, 131.2, and 159.3; m.s. ($M^+ - CH_3$): Calc. for $C_{20}H_{31}O_5Si$, *m/z* 395.1881; found, 395.1890.

*(*R (**14**) *and* S*)-1,4-Anhydro-1*-C-*(biphenyl-4-yl)-5*-O-[*(1,1-dimethylethyl)dimethylsilyl*]-*2,3*-O-*(1-methylethylidene)*-D-*ribitol* (27). — By the procedure used to prepare **11**, **6** (760 mg, 1.67 mmol) in 2,2,2-trifluorethanol (13 mL), sodium cyanoborohydride (315 mg, 5.00 mmol), and dichloroacetic acid afforded at room temperature (645 mg, 5.00 mmol), after flash chromatography (50 × 150 mm column of SiO_2, 10% ethyl acetate–petroleum ether), **14** and **21**.

Compound **14**. Yield 480 mg (66%), colorless white syrup, $[\alpha]_D^{23}$ −44° (*c* 1.5, chloroform), R_F 0.44 (SiO_2, 10% ethyl acetate–petroleum ether); $\nu_{max}^{CHCl_3}$ 3005, 2960, 2930, 2860, 1520, 1490, 1470, 1420, 1385, 1375, 1220, and 1080 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 0.08 (s, 6 H), 0.91 (s, 9 H), 1.23 (s, 3 H), 1.33 (s, 3 H), 3.78 (d, 2 H, *J* 3 Hz), 4.12 (t, 1 H, *J* 3 Hz), 4.80 (m, 2 H), 5.10 (d, 1 H, *J* 3 Hz), and 7.37 (m, 9 H); ^{13}C-n.m.r. ($CDCl_3$): δ 18.14, 24.73, 25.87, 26.17, 65.26, 83.24, 83.39, 84.31, 112.43, 126.65, 127.09, 127.82, 128.63, 136.06, 140.49, and 141.46; m.s. (M^+): Calc. for $C_{26}H_{36}O_4Si$, *m/z* 440.2383; found, 440.2366.

Compound **21**. Yield 122 mg (17%), colorless white syrup, $[\alpha]_D^{23}$ −53° (*c* 1.5, chloroform), R_F 0.54 (SiO_2, 10% ethyl acetate–petroleum ether); $\nu_{max}^{CHCl_3}$ 3015, 2995, 2960, 2930, 2860, 1600, 1490, 1470, 1460, 1380, 1370, 1250, and 1080 cm^{-1}; ^{1}H-n.m.r. (360 MHz, $CDCl_3$): δ 0.107 (s, 3 H), 0.117 (s, 3 H), 0.927 (s, 9 H), 1.381 (s, 3 H), 1.649 (s, 3 H), 3.884 (ddd, 2 H, *J* 16.5, *J* 7.2, *J* 3.6 Hz), 4.217 (dd, 1 H, *J* 7.2, *J* 3.6 Hz), 4.549 (dd, 1 H, *J* 6.5, *J* 5 Hz), 4.783 (dd, 1 H, *J* 6.5, *J* 3.6 Hz), 4.960 (d, 1 H, *J* 5 Hz), 7.338 (tt, *J* 7.2, *J* 1.4 Hz), and 7.435–7.590 (m, 8 H); ^{13}C-n.m.r. (90 MHz, $CDCl_3$): δ −5.42, −5.32, 18.33, 25.65, 25.90, 27.69, 63.45, 81.85, 84.62, 85.69, 87.22, 114.36, 126.18, 127.09, 128.70, 139.37, 140.63, and 141.04; m.s. ($M^+ - CH_3$): Calc. for $C_{25}H_{33}O_4Si$, *m/z* 425.2148; found, 425.2156.

1,4:5,8-Dianhydro-2,3-dideoxy-9-O-[*(1,1-dimethylethyl)dimethylsilyl*]-*6,7*-O-*(1-methylethylidene)*-D-[altro- (**15**) *and* allo]-*nono-1,3-dienitol* (**22**). — To a stirred solution of **7** (896 mg, 2.42 mmol) in 2,2,2-trifluorethanol (19 mL) at room temperature was added first sodium cyanoborohydride (465 mg, 7.27 mmol), and

then dichloroacetic acid (931 mg, 7.27 mmol). The mixture was stirred at room temperature for 10 min, sat. aq. $NaHCO_3$ (10 mL) was added, and the mixture was poured into water (150 mL). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure to give a white oil which was purified by flash chromatography (60 × 180 mm column of SiO_2, 10% ethyl acetate–petroleum ether) to give **15** and **22**.

Compound **15**. Yield 642 mg (73%), colorless white oil, $[\alpha]_D^{23}$ −58° (*c* 1.5, chloroform), R_F 0.45 (SiO_2, 10% ethyl acetate–petroleum ether); $\nu_{max}^{CHCl_3}$ 2980, 2960, 2940, 2900, 2840, 1540, 1520, 1360, 1340, 1310, 1220, 1180, 1120, and 980 cm^{-1}; ^{1}H-n.m.r. (360 MHz, $CDCl_3$): δ 0.065 (s, 6 H), 0.895 (s, 9 H), 1.327 (s, 3 H), 1.475 (s, 3 H), 3.740 (dd, 2 H, *J* 3.2, *J* 10.9 Hz), 3.824 (dd, 1 H, *J* 3.2, *J* 10.9 Hz), 4.197 (t, 1 H, *J* 3.2 Hz), 4.836 (dd, 1 H, *J* 4.3, *J* 6.1 Hz), 4.907 (d, 1 H, *J* 6.1 Hz), 5.222 (d, 1 H, *J* 4.3 Hz), 6.438 (d, 1 H, *J* 3.2 Hz), 7.344 (dd, 1 H, *J* 1.8, *J* 3.2 Hz), and 7.382 (d, 1 H, *J* 1.8 Hz); ^{13}C-n.m.r. (90 MHz, $CDCl_3$): δ −5.6, 18.1, 25.08, 25.86, 26.25, 65.25, 78.86, 82.34, 83.26, 84.04, 108.76, 110.30, 112.70, 141.91, 150.59; m.s. (M^+): Calc. for $C_{18}H_{30}O_5Si$, *m/z* 354.1862; found, 354.1856.

Compound **22**. Yield 210 mg (24%), colorless white oil, $[\alpha]_D^{24}$ −44° (*c* 1.5, chloroform), R_F 0.52 (SiO_2, 10% ethyl acetate–petroleum ether); $\nu_{max}^{CHCl_3}$ 2990, 2980, 2940, 2860, 1480, 1460, 1380, 1360, 1250, 1210, 1150, and 1080 cm^{-1}; ^{1}H-n.m.r. (360 MHz, $CDCl_3$): δ 0.01 (s, 3 H), 0.021 (s, 3 H), 0.865 (s, 9 H), 1.348 (s, 3 H), 1.557 (s, 3 H), 3.660 (dd, 1 H, *J* 11.2, *J* 4.7 Hz), 3.725 (dd, 1 H, *J* 11.2, *J* 4.7 Hz), 4.123 (dd, 1 H, *J* 6.5, *J* 4.7 Hz), 4.745 (dd, 1 H, *J* 5.0, *J* 4.7 Hz), 4.830 (dd, 1 H, *J* 6.5, *J* 5.0 Hz), 4.884 (d, 1 H, *J* 4.7 Hz), 6.308 (m, 2 H), and 7.359 (s, 1 H); ^{13}C-n.m.r. (90 MHz, $CDCl_3$): δ −5.38, −3.42, 18.37, 25.59, 25.90, 27.50, 63.36, 79.91, 82.30, 83.65, 85.03, 107.98, 110.23, 114.06, 142.61, and 152.24; m.s. (M^+): Calc. for $C_{18}H_{30}O_5Si$, *m/z* 354.1862; found, 354.1844.

The identity of **14** and **21** was confirmed by desilylating each to afford the known[15] compounds **9** and **24**.

*1,4:5,8-Dianhydro-2,3-dideoxy-6,7-*O*-(1-methylethylidene)-*D-altro-*non-1,3-dienitol* (**9**). — To a stirred solution of **19** (366 mg, 0.99 mmol) in oxolane at room temperature was added tetrabutylammonium fluoride (500 mg, 1.88 mmol). After 4 h at room temperature, the mixture was poured into ether (80 mL) and washed three times with water. The organic phase was dried ($MgSO_4$) and then evaporated under reduced pressure to give **9** (263 mg, 94%), colorless white syrup, R_F 0.40 (SiO_2, 50% ethyl acetate–petroleum ether); ^{1}H-n.m.r. ($CDCl_3$): δ 1.33 (s, 3 H), 1.47 (s, 3 H), 3.65 (d, 2 H, *J* 5 Hz), 4.22 (t, 1 H, *J* 5 Hz), 4.66–4.90 (m, 2 H), 5.10 (d, 3 Hz), 6.39 (dd, 1 H, *J* 3.5, *J* 1.5 Hz), 6.50 (d, 1 H, *J* 3.5 Hz), and 7.45 (s, 1 H); ^{13}C-n.m.r. ($CDCl_3$): δ 24.97, 26.14, 62.30, 78.43, 81.75, 82.57, 84.15, 109.32, 110.49, 113.16, 142.16, and 149.84; m.s. (M^+): Calc. for $C_{12}H_{16}O_5$, *m/z* 240.0997; found, 240.0994.

*1,4:5,8-Dianhydro-2,3-dideoxy-6,7-*O*-(1-methylethylidene)-*D-allo-*non-1,3-dienitol* (**24**). — To a stirred solution of **22** (60 mg, 0.16 mmol) in acetonitrile (4 mL) at −5° was added 48% aqueous HF (0.10 mL, 2.4 mmol). After 15 min at −5°,

sat. aq. $NaHCO_3$ (3 mL) was added, and the mixture was poured into dichloromethane (80 mL) and washed with water (30 mL). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure to give **22** (28 mg, 73%), colorless white syrup; ^{1}H-n.m.r. (360 MHz, $CDCl_3$): δ 1.340 (s, 3 H), 1.558 (s, 3 H), 3.619–3.685 (m, 2 H), 4.174 (dd, 1 H, *J* 7.2, *J* 5.0 Hz), 4.765 (m, 1 H), 4.861 (t, 1 H, *J* 5.0 Hz), 4.910 (d, 1 H, *J* 4.7 Hz), 6.350 (m, 2 H), and 7.394 (s, 1 H); ^{13}C-n.m.r. (90 MHz, $CDCl_3$): δ 25.430, 27.392, 62.896, 80.058, 81.915, 83.798, 85.079, 108.558, 110.395, 114.444, 143.089, and 151.773.

*1,4:5,8-Dianhydro-2,3-dideoxy-9-*O*-[(1,1-dimethylethyl)dimethylsilyl]-6,7-*O*-(1-methylethylidene)-*D*-(*altro*-)-nono-1,3-dienitol* (**15**) *by reduction of* **7** *in methanol.* — By the procedure used to prepare **13**, **7** (70 mg, 0.19 mmol) in methanol (0.5 mL) was treated at 0° with 4-toluenesulfonic acid hydrate (65 mg, 0.34 mmol) and sodium cyanoborohydride (75 mg, 1.19 mmol) at 0° for 10 s, and then the reaction quenched with sat. aq. $NaHCO_3$ (2 mL). The mixture was poured into ether (30 mL) and washed with sat. aq. $NaHCO_3$ (20 mL) and water (20 mL). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure to give, after flash chromatography (20 × 140 mm column of SiO_2, 20% ethyl acetate–petroleum ether), **15** (41 mg, 62%), colorless white oil, identical with the material described earlier.

4,4′-(Ethylenedioxy)dibromobenzene (**25**). — To a stirred solution of 1,2-bis(phenoxy)ethane (15 g, 70.1 mmol) in glacial acetic acid (530 mL) at room temperature was aded Br_2 (23.5 g, 147 mmol). After stirring at room temperature for 1 h, 5% aqueous $Na_2S_2O_3$ solution was added. Dilution of the mixture with water (400 mL) afforded a crude product which was collected by filtration and recrystallized from chloroform–ethanol to give **25** (22.3 g, 86%), lustrous white plates, m.p. 125–126.5° (lit.[22] m.p. 131–132°).

*4,4′-(Ethylenedioxy)bis[5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-2,3-*O*-(1-methylethylidene)-*D*-ribofuranosyl]benzene* (**27**). — To a vigorously stirred solution of 1.8M *tert*-butyllithium (18.2 mL, 32.8 mmol) in pentane at −78° was added dropwise a solution of dibromide **25** (2.98 g) in oxolane (70 mL). After being stirred at −78° for 1 h, the yellow solution was warmed to −15° for 10 min and then again cooled to −78°. To this solution of 4,4′-(ethylenedioxy)dilithiobenzene (**26**) was added, dropwise, over 10 min, a precooled (−70°) solution of **1** (5.074 g, 16.8 mmol) in oxolane (50 mL). The mixture was stirred at −78° for 6 h, then methanol (1 mL) was added, the mixture was allowed to warm to room temperature, and then poured into ether (500 mL) and washed three times with water (200 mL). The organic phase was separated, dried ($MgSO_4$), and evaporated under reduced pressure to give **27** (6.55 g, 100%), white foam; $[\alpha]_D^{23}$ −51° (*c* 1.5, chloroform), R_F 0.22 (SiO_2, 20% ethyl acetate–petroleum ether); $\nu_{max}^{CCl_4}$ 3590, 3550–3250, 2960, 2930, 2860, 1610, 1515, 1380, 1370, 1240, and 1080 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 7.64 (d, 2 H, *J* 8.6 Hz), 6.91 (d, 2 H, *J* 8.6 Hz), 5.15 (s, 1 H), 4.89 (d, 1 H, *J* 5.4 Hz), 4.60 (d, 1 H, *J* 5.4 Hz), 4.43 (br. s, 1 H), 4.29 (s, 2 H), 3.88 (dd, 1 H, *J* 10.8, *J* 2.5 Hz), 3.82 (dd, 1 H, *J* 10.8, *J* 2.5 Hz), 1.39 (s, 3 H), 1.24 (s, 3 H), 0.94 (s, 9 H), and 0.16

(s, 6 H); ^{13}C-n.m.r. ($CDCl_3$): δ 158.52, 131.83, 128.31, 114.22, 113.65, 112.53, 106.86, 88.49, 86.08, 82.00, 66.46, 64.82, 26.46, 25.80, 24.87, 18.24, and −5.64. For quantitative analysis, a portion of this product was converted into the corresponding methyl glycoside **28** by the action of methanolic trifluoroacetic acid. The glycoside crystallized from the solution and was recrystallized from ethyl acetate–methanol, m.p. 107–108.5°, $[\alpha]_D^{23}$ −67° (*c* 1.5, chloroform), R_F 0.64 (SiO_2, 20% ethyl acetate–petroleum ether); $\nu_{max}^{CCl_4}$ 2980, 2930, 2860, 1610, 1515, 1380, 1370, 1240, and 1100 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 7.394 (d, 2 H, *J* 8.6 Hz), 6.928 (d, 2 H, *J* 8.6 Hz), 4.805 (d, 1 H, *J* 5.8 Hz), 4.643 (d, 1 H, *J* 5.8 Hz), 4.318 (br. s, 2 H), 3.757 (appar. t, 2 H), 2.980 (s, 3 H), 1.296 (s, 3 H), 1.229 (s, 3 H), 0.918 (s, 9 H), and 0.095 (s, 6 H); ^{13}C-n.m.r. ($CDCl_3$): δ 158.53, 129.42, 128.93, 113.98, 112.37, 111.65, 87.46, 86.60, 82.79, 66.45, 63.91, 49.06, 26.48, 25.92, 25.22, 18.34, and −5.28.

Anal. Calc. for $C_{44}H_{70}O_{12}Si_2$: C, 62.38; H, 8.33. Found: C, 61.69; H, 8.41.

*4,4'-(Ethylenedioxy)bis(1*R*,1'*R*)-1,4-anhydro-5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-2,3-O-(1-methylethylidene)-*D*-ribit-1-yl)benzene* (29). — To a solution of **27** (6.55 g, 8.00 mmol) in methanol (54 mL) at 0° was added first 4-toluenesulfonic acid monohydrate (5.43 g, 28.5 mmol), and then sodium cyanoborohydride (3.39 g, 53.6 mmol). The mixture was stirred at 0° for 7 min, and then poured in sat. aq. $NaHCO_3$ (200 mL). Ether (500 mL) was added and the organic phase was washed with water (3 × 200 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give (**29**) (6.40 g, 100%), white foam, $[\alpha]_D^{23}$ −71° (*c* 1.5, chloroform), R_F 0.22 (SiO_2, 20% ethyl acetate–petroleum ether); $\nu_{max}^{CCl_4}$ 2995, 2960, 2930, 2860, 1590, 1510, 1380, 1370, 1240, and 1080 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 7.306 (d, 2 H, *J* 8.6 Hz), 6.921 (d, 2 H, *J* 8.6 Hz), 5.179 (d, 1 H, *J* 4 Hz), 4.934 (d, 1 H, *J* 6.1 Hz), 4.758 (dd, 1 H, *J* 6.1, *J* 4 Hz), 4.289 (s, 2 H), 4.237 (t, 1 H, *J* 3.2 Hz), 3.848 (dd, 1 H, *J* 10.8, *J* 3.2 Hz), 3.789 (dd, 1 H, *J* 10.8, *J* 3.2 Hz), 1.471 (s, 3 H), 1.294 (s, 3 H), 0.935 (s, 9 H), and 0.090 (s, 6 H); ^{13}C-n.m.r. ($CDCl_3$): δ 158.25, 129.42, 128.68, 114.16, 112.26, 84.01, 83.27, 83.12, 66.54, 65.08, 26.18, 25.8, 24.70, 18.08, and −5.58; m.s.: Calc. for $C_{42}H_{66}O_{10}Si$, *m/z* 786.4194; found, 786.4170.

*4,4'-(Ethylenedioxy)bis[(1*R*,1'*R*)-1,4-anhydro-2,3-O-(1-methylethylidene)-*D*-ribit-1-yl]benzene* (**30**). — To a stirred solution of **29** (5.786 g, 7.36 mmol) in acetonitrile (50 mL) at 0° was added 48% aqueous HF (625 mg, 18 mmol). The mixture was stirred at 0° for 40 min, then poured into a mixture of sat. aq. $NaHCO_3$ (25 mL) and ethyl acetate (200 mL), and then washed twice with water (200 mL). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure to give **30**, white powder which crystallized from ethanol–water (3.292 g, 80%), m.p. 145.5–146.5°, $[\alpha]_D^{23}$ −96.9° (*c* 1.5, chloroform),, R_F 0.22 (SiO_2, ethyl acetate); $\nu_{max}^{CHCl_3}$ 3600, 3620–3500, 3000, 2960, 2860, 1510, 1380, 1370, 1220, 1110, and 1060 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 7.333 (d, 2 H, *J* 8.6 Hz), 6.935 (d, 2 H, *J* 8.6 Hz), 4.954 (d, 1 H, *J* 3.6 Hz), 4.741 (dd, 1 H, *J* 6.1, *J* 3.6 Hz), 4.709 (d, 1 H, *J* 6.1 Hz), 4.323 and 4.303 (overlapping s, 5 H), 3.674 (d, 2 H, 5.8 Hz), 1.481 (s, 3 H), and 1.278 (s, 3 H); ^{13}C-n.m.r. ($CDCl_3$): δ 158.48, 128.84, 128.62, 114.30, 112.77, 84.41, 82.69, 82.46, 66.61, 62.07, 26.27, and 24.80.

Anal. Calc. for $C_{30}H_{38}O_{10}$: C, 64.50; H, 6.86. Found: C, 64.18; H, 6.77.

*4,4'-(Ethylenedioxy)bis(1*R*,1*R*')-1,4-anhydro-5-deoxy-5-[(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-2,3-*O*-(1-methylethylidene)-*D*-ribit-1-yl]benzene* (**31**). — To a stirred solution of **30** (2.02 g, 3.62 mmol) in oxolane (30 mL) at room temperature was added triphenylphosphine (1.90 g, 7.24 mmol), phthalimide (1.07 g, 7.24 mmol), and diethyl azodicarboxylate (1.26 g, 7.24 mmol). The mixture was heated at reflux for 3.5 h, cooled, and then poured into 50% ether–ethyl acetate (200 mL). The organic phase was washed with water (200 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The oily residue was purified by flash chromatography (50 × 180 mm column of SiO_2, ethyl acetate) to give a powder which crystallized from chloroform–methanol to give **31** (2.09 g, 71%), white powder, m.p. 212–214°, $[\alpha]_D^{23}$ 49° (*c* 1.5, chloroform), R_F 0.58 (SiO_2, ethyl acetate); $\nu_{max}^{CHCl_3}$ 3000, 2840, 1775, 1715, 1515, 1400, 1380, 1370, and 1220 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 7.820 (dd, 2 H, *J* 7.8, *J* 2.9 Hz), 7.692 (dd, 2 H, *J* 7.8, *J* 2.9 Hz), 7.346 (d, 2 H, *J* 8.6 Hz), 6.900 (d, 2 H, *J* 8.6 Hz), 5.085 (d, 1 H, *J* 3.6 Hz, 4.844 (dd, 1 H, *J* 5.8, *J* 3.6 Hz), 4.732 (d, 1 H, 5.8 Hz), 4.589 (m, 1 H), 4.276 (s, 2 H), 3.900 (dd, 1 H, *J* 13.7, *J* 9.7 Hz), 3.733 (dd, 1 H, *J* 13.7, *J* 6.1 Hz), 1.472 (s, 3 H), and 1.279 (s, 3 H); ^{13}C-n.m.r. ($CDCl_3$): δ 168.04, 158.48, 133.93, 132.12, 129.14, 128.13, 123.33, 114.24, 112.77, 83.38, 82.3, 81.65, 80.57, 66.55, 37.18, 26.12, and 24.76.

Anal. Calc. for $C_{46}H_{44}O_{12}N_2 \cdot 2\ CH_3OH$: C, 65.45; H, 5.91. Found: C, 65.36; H, 5.27.

*4,4'-(Ethylenedioxy)bis(1*R*,1'*R*)-5-amino-1,4-anhydro-5-deoxy-2,3-O-(1-methylethylidene)-*D*-ribit-1-yl)benzene* (32). — To a stirred solution of **31** (2.09 g, 2.56 mmol) in a mixture of benzene (5 mL) and ethanol (12 mL) at room temperature was added hydrazine hydrate (2.06 g, 41.2 mmol). The mixture was heated at reflux, after which time the initially clear white solution became a white paste. After 16 h at reflux, the mixture was poured into 50% ether–ethyl acetate (200 mL) and washed twice with M NaOH solution. The organic layer was dried ($MgSO_4$) and then evaporated under reduced pressure to give a white oil. Flash chromatography (30 × 180 mm column of SiO_2, 2% triethylamine–methanol) afforded **32** (808 mg, 78%), clear white oil, $[\alpha]_D^{23}$ −81° (*c* 1.5, chloroform), R_F 0.22 (SiO_2, 2% triethylamine–methanol); $\nu_{max}^{C_6H_6}$ 3700, 3640, 3070, 3020, 1620, 1530, 1480, 1390, 1240, and 1180 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 7.348 (d, 2 H, *J* 8.6 Hz), 6.935 (d, 2 H, *J* 8.6 Hz), 4.860 (d, 1 H, *J* 3.6 Hz), 4.730 (dd, 1 H, *J* 5.8, *J* 3.6 Hz), 4.625 (d, 1 H, *J* 5.8 Hz), 4.300 (s, 2 H), 4.180 (dd, 1 H, *J* 9.0, *J* 4.7 Hz), 2.843 (dd, 1 H, *J* 13.3, *J* 4.7 Hz), 2.729 (dd, 1 H, *J* 13.3, *J* 4.7 Hz), 1.486 (s, 3 H), and 1.275 (s, 3 H); ^{13}C-n.m.r. ($CDCl_3$): δ 158.34, 128.77, 128.55, 114.46, 112.54, 85.70, 83.58, 82.49, 81.41, 66.49, 42.08, 26.16, and 24.72; m.s. ($M^+ - CH_3$): Calc. for $C_{29}H_{37}O_8N_2$, *m/z* 541.2550; found, 541.2561.

*[3a*S*-(3a*R**,4*S**,17*S**,17a*R**,20a*S**,21*S**,32*S**,32a*S**)]-3a,4,10,11,17,17a,20a,21,22,23,30,31,32,32a-Tetradecahydro-2,2,19,19-tetramethyl-4,32:17,21-diepoxy-5,8:13,16:25,28-triethenobis[1,3]dioxolo[4,5-j:4',5'-x][1,3,14,21]dioxadiaza-*

cyclotriacontine-24,29-dione (**34**). — To a solution of triethylamine (2.03 g, 20.0 mmol) in toluene (54 mL) at 26° was added, simultaneously, over a period of 13 h, a solution of **32** (1.11 g, 2.00 mmol) in oxolane (36 mL) and a solution of terephthaloyl chloride (406 mg, 2.00 mmol) in toluene (36 mL). The resulting solution was evaporated under reduced pressure to a white powder which was washed with water (100 mL) and ether (50 mL), and then dried under vacuum to give a white powder (662 mg) which was dissolved with dichloromethane (25 mL) and the solution filtered. Removal of the dichloromethane and crystallization from chloroform–methanol gave **34** (207 mg, 15%), amorphous white powder, homogeneous by t.l.c., m.p. >300° (chars), $[\alpha]_D^{23}$ 58° (*c* 1.5, chloroform), R_F 0.16 (SiO_2, dichloromethane), R_F 0.76 (SiO_2, 10% methanol–dichloromethane); $\nu_{max}^{CHCl_3}$ 3005, 2830, 1660, 1610, 1510, 1420, 1380, 1375, 1220, 1100, and 1080 cm^{-1}; ^{1}H-n.m.r. (50% Me_2SO–$CDCl_3$, 65°, 200 MHz): δ 7.732 (s, 2 H), 7.162 (d, 2 H, *J* 8.6 Hz), 6.772 (d, 2 H, *J* 8.6 Hz), 4.783 (dd, 1 H, *J* 5.8, *J* 3.4 Hz), 4.682 (d, 1 H, *J* 3.4 Hz), 4.657 (d, 1 H, *J* 5.8 Hz), 4.292 (br. s, 4 H), 4.242 (br. d, 1 H, *J* 9 Hz), 3.412 (d, 1 H, *J* 2.4 Hz), 3.395 (d, 1 H, *J* 9 Hz), 1.402 (s, 3 H), 1.248 (s, 3 Hz); ^{13}C-n.m.r. (DMSO): δ 228.52, 166.43, 156.86, 137.01, 129.09, 128.71, 126.92, 114.40, 111.17, 82.99, 81.54, 79.64, 79.42, 65.22, 38.01, 25.96, and 24.49; m.s.: Calc. for $C_{38}H_{42}O_{10}$, *m/z* 686.2839; found, 686.2823.

[3aS-(3aR,4S*,17S*,17aR*,20aS*,21S*,32S*,32aS*)]-3a,4,10,11,17,17a,20a,21,22,23,30,31,32,32a-Tetradecahydro-2,2,19,19-tetramethyl-4,32:17,21-diepoxy-5,8:13,16:25,28-triethenobis[1,3]dioxolo[4,5-j:4′,5′-x][1,4,14,21]dioxadiazacyclotriacontine-24,29,dione* (**35**). — A solution of **32** (36 mg, 0.052 mmol) in 70% acetic acid (3 mL) was heated at 70° for 72 h. The mixture was cooled, and the solvent removed under reduced pressure to give a tan powder which was purified by flash chromatography (30 × 180 mm column of SiO_2, 73% dichloromethane–25% methanol–2% water) to give **33** (21 mg, 66%), amorphous white powder, $[\alpha]_D^{23}$ −1.4° (*c* 1.0, 50% methanol–chloroform), R_F 0.65 (SiO_2, 73% dichloromethane–25% methanol–2% water); $\nu_{max}^{Me_2SO}$ 3700–3150, 3000, 2915, 1655, 1440, and 1420 cm^{-1}; ^{1}H-n.m.r. [50% ($^2H_4$)methanol–(^{2}H)chloroform]: δ 7.555 (s, 2 H), 7.032 (d, 2 H, *J* 8.6 Hz), 6.637 (d, 2 H, *J* 8.6 Hz), 4.736 (d, 1 H, *J* 1.8 Hz), 4.057 (d, 1 H, *J* 9.4 Hz), 4.003 (d, 1 H, *J* 9.4 Hz), 3.901 (br. s, 2 H), 3.823 (d, 1 H, *J* 13.0 Hz), and 3.061–3.000 (m, 2 H); ^{13}C-n.m.r. [50% ($^2H_4$)methanol–(^{2}H)chloroform): δ 167.64, 157.43, 137.1, 130.12, 128.89, 126.94, 115.12, 81.82, 79.35, 75.31, 73.24, 66.00, and 42.60.

Synthesis and deprotection of [3aS-(3aR,4S*,17S*,17aR*,20aS*,21S*,24aS*,27aS*,31S*,31aS*)]-3a,4,10,11,17,17a,20a,21,22,23,24a,27a,29,30,31a-hexadecahydro-2,2,19,19-tetramethyl-4,31:17,21-diepoxy-5,8:13,16-diethenotris[1,3]dioxolo-[4,5-j:4′,5′-p:4″,5″-y][1,4,14,19]dioxadiazacyclooctacosine-24,28-dione (methylene tartramide macrocyle)* (**33**). — To a solution of toluene (50 mL) containing triethylamine (1.30 g, 12.9 mmol) at 23° were added, simultaneously, over 18 h, a solution of **32** (1.07 g, 1.92 mmol) and triethylamine (726 mg, 7.19 mmol) in oxolane (34 mL) and a solution of 2,3-*O*-methylenetartaric acid dichloride[25] (380

mg, 1.92 mmol) in toluene (35 mL). After the addition was complete, the mixture was stirred an additional 2 h, and then water (20 mL) was added and stirring continued for 10 min. The mixture was poured into 4:1 ethyl acetate–dichloromethane (250 mL). A small amount of insoluble material was removed by filtration and the liquid organic phase was washed twice with M HCl (100 mL), and twice with sat. aq. $NaHCO_3$ (100 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. Flash chromatography (40 × 180 mm column of SiO_2, 45% ethyl acetate–45% dichloromethane–10% methanol) gave the protected macrocycle (146 mg, 11%), m.p. >260° (chars), $[\alpha]_D^{23}$ −43° (*c* 0.85, chloroform), R_F 0.51 (SiO_2, 45% ethyl acetate–45% dichloromethane–10% methanol); $\nu_{max}^{CHCl_3}$ 2980, 2930, 1690, 1610, 1515, 1380, 1370, 1220, and 1100 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 7.221 (d, 2 H, *J* 8.6 Hz), 6.776 (d, 2 H, *J* 8.6 Hz), 4.871 (s, 1 H), 4.800 (dd, 1 H, *J* 5.8, *J* 3.6 Hz), 4.649 (d, 1 H, *J* 3.6 Hz), 4.618 (s, 1 H), 4.582 (d, 1 H, *J* 5.8 Hz), 4.363 (s, 2 H), 4.260 (dd, 1 H, *J* 10.8, 4.7 Hz), 3.46–3.54 (m, 1 H), and 3.25–3.33 (m, 1 H); ^{13}C-n.m.r. (Me_2SO): δ 168.83, 157.23, 129.32, 128.78, 117.56, 115.04, 111.32, 95.42, 82.92, 81.49, 80.80, 79.73, 77.05, 66.49, 26.06, and 24.57.

A solution of the protected macrocycle (31 mg, 0.045 mmol) in 70% acetic acid (4 mL) was heated at 70° for 12 h. The solvent was removed under reduced pressure and the residual oil purified by chromatography on SiO_2 (5 g, 20% methanol–dichloromethane) to give **33** (25.5 mg, 93%), glass, $[\alpha]_D^{23}$ −11.3° (*c* 0.95, methanol), R_F 0.46 (SiO_2, 20% methanol–dichloroform); $\nu_{max}^{Me_2SO}$ 3700–3150, 2995, 2810, 1660, 1440, 1405, 1310, and 1080 cm^{-1}; ^{1}H-n.m.r. [D_2O, sodium 4,4-dimethyl-4-sila(2,3-$^2H_4$)pentanoate as external reference]: δ 7.171 (d, 2 H, *J* 8.6 Hz), 6.824 (d, 2 H, *J* 8.6 Hz), 5.238 (s, 2 H), 5.077 (d, 1 H, *J* 2.5 Hz), 4.610 (s, 1 H), 4.454 (br. s, 2 H), 4.229–4.287 (m, 2 H), 4.135 (td, 1 H, *J* 7.9, *J* 2.5 Hz), 3.648 (dd, 1 H, *J* 14.4, *J* 2.5 Hz), and 3.504 (dd, 1 H, *J* 14.4, *J* 7.9 Hz); ^{13}C-n.m.r. [D_2O, sodium 4,4-dimethyl-4-sila(2,3-$^2H_4$)pentanoate as external reference]: δ 173.87, 159.68, 132.94, 130.96, 119.06, 99.60, 84.62, 82.16, 80.32, 77.25, 76.07, 70.24, and 44.48.

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SELECTIVE MONO-CLAISEN REARRANGEMENT OF CARBOHYDRATE GLYCALS. A CHEMICAL CONSEQUENCE OF THE VINYLOGOUS ANOMERIC EFFECT

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ABSTRACT

The mono-Claisen rearrangement of carbohydrate glycals is demonstrated to be a synthetically useful and mechanistically significant reaction. Addition of per-*O*-acetyl glycal–*tert*-butyldimethylchlorosilane mixture to lithium diisopropylamide generated a bis (or tris)ketenesilylacetal which, upon heating, underwent smooth mono-Claisen rearrangement to provide a *C*-glycosyl compound after methylation. A second apparently similar Claisen rearrangement required significantly higher temperatures in all cases. Thus, similar hydroxy groups were differentiated without resort to selective protection. A stereoelectronic rationale based on the newly-introduced vinylogous anomeric effect (VAE) is put forth to explain the accelerated Claisen rearrangements of these glycals. Molecular orbital and resonance descriptions of the VAE are included, and the VAE is also used to rationalize ground-state conformational preferences of carbohydrate glycals. The *C*-glycosyl compounds produced by mono-Claisen rearrangement were suitable for Pd(0)-catalyzed allylic alkylations, providing an unusually facile entry into the pseudomonic acid-ring systems. A nine-step synthesis of a known precursor of pseudomonic acid C is reported.

INTRODUCTION

The aliphatic Claisen rearrangement of allyl vinyl ethers to γ,δ-unsaturated carbonyl groups has become one of the most powerful and versatile tools for stereocontrolled, carbon–carbon bond formation in organic synthesis[1]. Variations of this sigmatropic rearrangement have permitted easy access to the required allyl vinyl ethers and dramatically lowered the temperature of the transposition by modification of substituents[2]. The Ireland ester enolate–Claisen procedure is perhaps the mildest and most generally useful variant now available[3]. Indeed, the

*Alfred P. Sloan Foundation Fellow, 1985–87; Dreyfus Teacher-Scholar, 1986–91; Eli Lilly Grantee, 1985–87; Merck Young Faculty Development Awardee, 1986.

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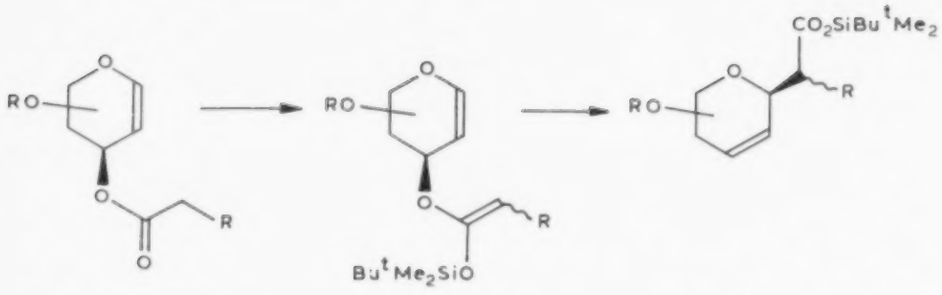


Scheme 1.

Ireland–Claisen rearrangement is almost ideal for the conversion of readily available carbohydrate glycals to biologically important *C*-glycosyl compounds (Scheme 1), and many elegant examples of the utility of this transformation have been provided by the Ireland school in both the pyran and furan series[4].

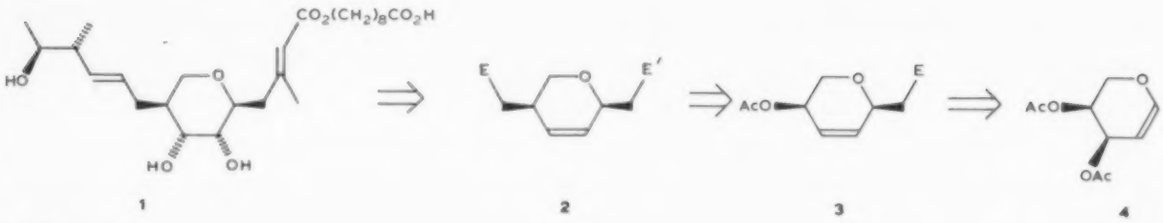
One potential drawback in the application of the Ireland–Claisen rearrangement is the (perceived) need for selective protection of the remaining hydroxyl groups in the carbohydrate as a means of rigorous chemical differentiation[4]. Such selective protection–deprotection sequences are common and lengthy, and can detract from the utility of carbohydrates as starting materials for natural products synthesis[5]. Development of reactions which differentiate between hydroxyl groups without selective protection is then an important goal in this field.

We were prompted to address this problem by a strategy for the synthesis of pseudomonic acid C (**1**) outlined in Scheme 2*. The pseudomonic acids are a relatively but small important family of antibiotics which possess the novel *C*-glycopyranosyl ring nucleus[7].

The strategy calls for the sequential transformation of the two C–OAc bonds of 3,4-di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-L-*erythro*-pentenitol (**2**) into two C–C bonds in pseudomonic acid C (**1**). The first transformation (**4**→**3**) requires the retention of relative stereochemical orientation coupled with transposition of allylic regioselectivity, whereas the second step (**3**→**2**) requires the retention of both stereo- and regio-selectivity. Finally, *cis*-hydroxylation from the less-hindered face of **2** and side-chain elaboration would provide **1**. Our approach is fundamentally different from the more common method of synthesis of pseudomonic acids from carbohydrates. In this generalized approach, outlined in Scheme 3, C-2–O and C-3–O bonds derived from the carbohydrate molecule are carried through the sequence intact, while the remaining hydroxy (or hydroxymethyl) substituents are used as handles for side-chain introduction†. Although this approach may appear more straightforward on the surface, selective protection–deprotection and activation of the various hydroxy groups is required. These reactions do add to the length of the

*Portions of this work have been reported in preliminary form[6].

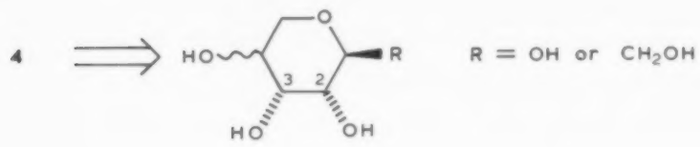
†For racemic synthesis, see refs. 8–11. For nonracemic synthesis, see refs. 12–15. For synthetic approach, see refs. 17–18.



1 2 3 4

Scheme 2.

synthesis, even though they are frequently routine and high-yielding. We will demonstrate that the approach outlined in Scheme 2 provides a direct route from the readily available L-arabinal derivative **4** to the pseudomonic acid ring nucleus. As an added bonus, we note that D- and L-arabinose are equally inexpensive sugars, so that either enantiomeric series may be accessed.



Scheme 3.

Clearly the Ireland–Claisen rearrangement is well suited for the initial key C–O to C–C conversion (**4** →**3**) since both stereo and regio conditions are insured. However, the problem of differentiation of the two similar secondary acetates in **4** immediately arises. To avoid the problem of differentiation by protection, we have addressed the possibility of a selective mono-Claisen rearrangement of the bis(ketenesilyl)acetal derived from **4**. We now wish to report the full details of our study which show (a) that the mono-Claisen rearrangement of carbohydrate glycal polyketene acetals is a useful and general reaction; (b) that this selective Claisen rearrangement is promoted by an accelerating substituent effect of the pyran oxygen atom; (c) that this acceleration can be interpreted as a chemical consequence of the vinylogous anomeric effect (VAE); and, finally, (d) that the products of this rearrangement are suitable for further selective transformations including rapid construction of the ring nucleus of the pseudomonic acids[6].

RESULTS AND DISCUSSION

In the context of the synthetic approach to pseudomonic acid C (**1**), the selective Ireland–Claisen rearrangement was first investigated with readily available **4** (ref. 19). Generation of the bisester enolate by dropwise addition of **4** to lithium diisopropylamide (LDA), followed by silylation with *tert*-butylchlorodi-

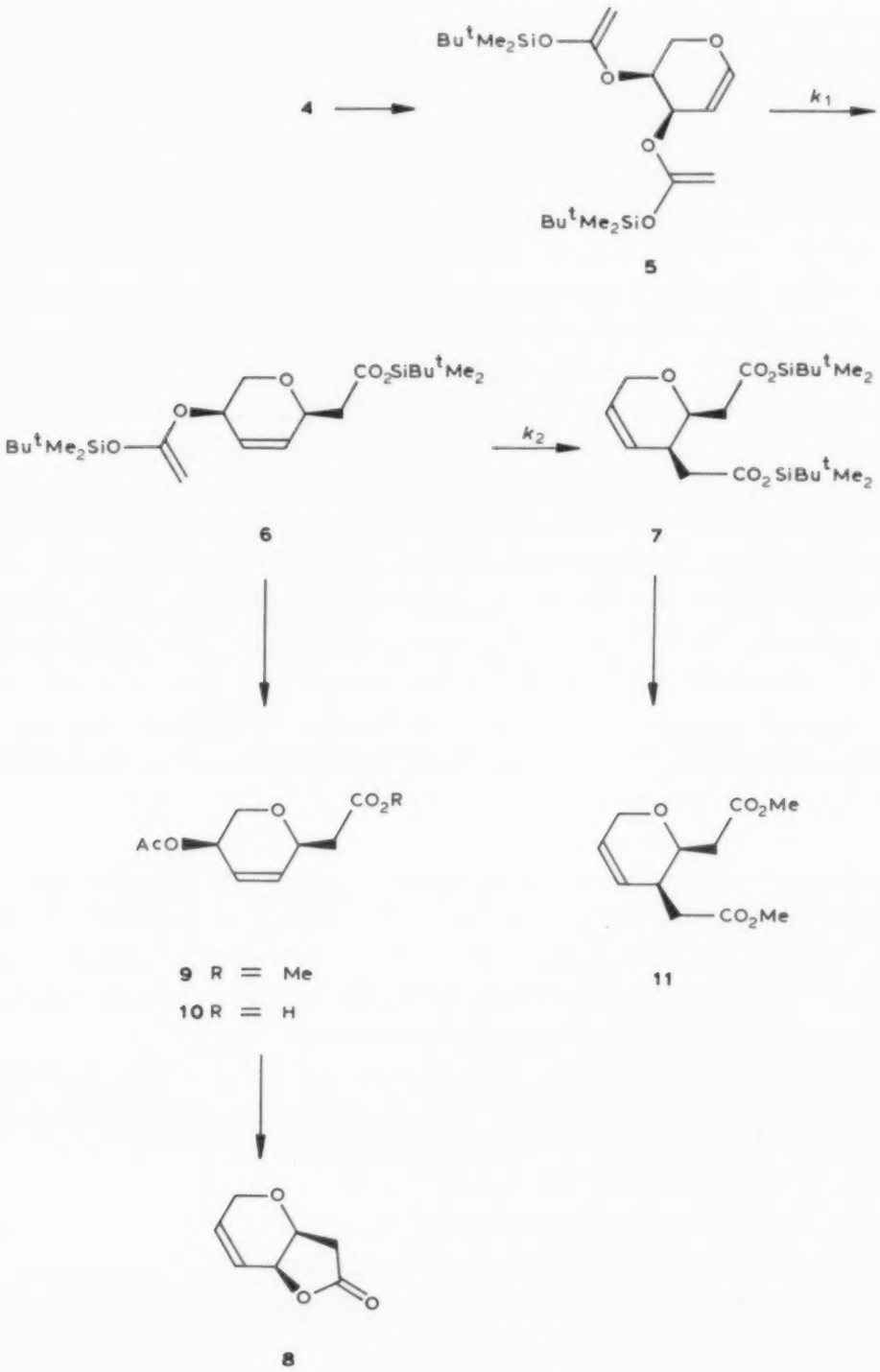
methylsilane produced a near quantitative yield of bis(silylated) material after pentane extraction. Whereas the major product (85–90%) was the bis(ketenesilyl)acetal **5**, small proportions of at least two other materials were present. Though it was strongly suspected that these were the two possible α-silyl ester ketenesilyl acetals resulting from mono *C*-silylation, the identity of the minor products was not pursued. Silylation with chlorotrimethylsilane resulted in bis(α-silyl) ester formation, and further attempts to improve the purity of the crude bis(ketenesilyl)acetal **5** by variation of the solvent, counter-ion, additive, and silylating agent were not encouraging. In general, the bis(silylated) product was rearranged without purification.

Warming of crude bis(ketenesilyl)acetal **5** for 6 h at 60° in $CDCl_3$ or C_6D_6 resulted in smooth conversion to the mono-Claisen rearrangement product **6** as indicated by ^{1}H-n.m.r. spectroscopy. In a preparative experiment, the crude rearrangement product was directly subjected to desilylation and methylation[6]. Following flash chromatography, acetate **9** was isolated in 60% yield, along with a small amount (<5%) of diester **11** resulting from the second Claisen rearrangement (**6** →**7**). A small proportion of **4** (5–7%) was also recovered. This is believed to have resulted from *C*-silylation of OAc-4, since prolonged heating at higher temperatures did not decrease the yield of this product. Alternatively, brief desilylation with potassium fluoride provides the unstable acid **10**, also in ~60% yield. Acid **10** could not be purified owing to its tendency to liberate acetic acid to form the vinyl lactone **8**. Racemic **8** is an intermediate in the Raphael synthesis[11] of pseudomonic acid C. Although **10** rearranged on standing at room temperature, the crude acid could be used immediately for subsequent transformations *(vide infra)*.

We were most pleased to discover that this selective mono-Claisen rearrangement process was practical. Indeed, the 60% yield of isolated **9** from **4** was quite satisfactory considering the number of operations in this sequence and the transformations accomplished. Note that a new carbon–carbon bond had been selectively formed and two similar secondary acetates had been differentiated in the process without resort to protection.

The tandem-Claisen product **7** was formed readily at higher temperatures. Heating of **5** in toluene at reflux, followed by desilylation–methylation as described above, provided the diester **11** in 45% yield. It is noted that such tandem-Claisen products may be synthetically useful in their own right.

We were most intrigued by this significant difference in rate between two apparently similar Claisen rearrangements. To determine the generality of the sequence outlined in the sequence **4** →**11**, the selective mono-Claisen rearrangement of related glycals was investigated. Initial attempts to doubly deprotonate 3,4-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*threo*-pent-1-enitol (**12**), according to the procedure used for **4**, met with disastrous results. Dropwise addition of **12** to lithium diisopropylamide at −78°, followed by quenching with *tert*-butylchlorodimethylsilane, provided a mixture containing bis(ketenesilyl)acetal **13** (~25%), contaminated with at least six or seven other products. Extensive variation of solvent,

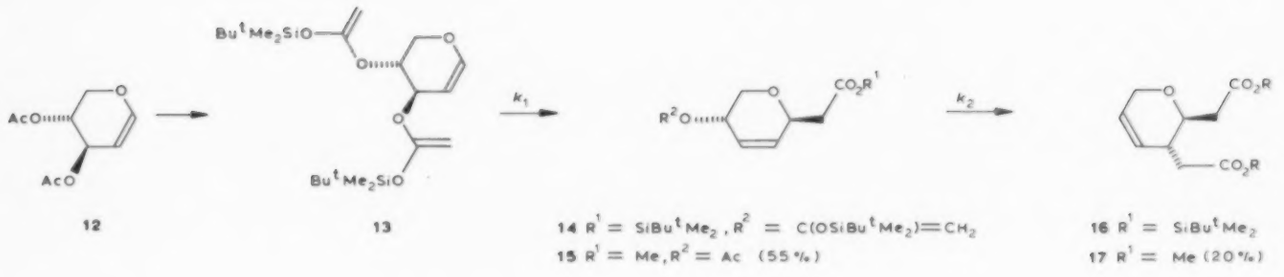

Bu^{t}Me$_2$SiO
4
k_1
Bu^{t}Me$_2$SiO
5
CO$_2$SiBu^{t}Me$_2$
Bu^{t}Me$_2$SiO
k_2
CO$_2$SiBu^{t}Me$_2$
CO$_2$SiBu^{t}Me$_2$
6
7
CO$_2$R
AcO
CO$_2$Me
CO$_2$Me
9 R = Me
10 R = H
11
8

temperature, silylating agent, base, or additive was not beneficial. At this time, our attention was directed to a report by Krizan and Martin[20] of the ortho-lithiation of benzonitrile with LDA in the presence of chlorotrimethylsilane. These results clearly demonstrated that quenching of LDA with the chloride was slower than deprotonation of relatively acidic protons by LDA. This technique has provided a general solution for the formation of [bis (and tris)ketene]silylacetals. Thus, dropwise addition of a mixture of both *tert*-butylchlorodimethylsilane (2 equiv.) and **12** (1 equiv.) to LDA (2 equiv.) at −78° in oxolane provided a near quantitative yield of bis(silyl)ated compound **13**. In this manner, an ester enolate is trapped by silylation immediately upon generation, and possible side-reactions are superseded. As described before, the major product (85–90%) was the bis(ketenesilyl)acetal and the minor products were believed to be mono-*C*-silylated ketenesilylacetals. All subsequently described bis(ketenesilyl)acetals were formed by this procedure. Several deprotonations entirely analogous to the method described above have been reported during the course of our work[21]. It is clear that this is a valuable technique for rapid trapping of anions.

With a procedure for bis(ketenesilyl)acetal formation in hand, a variety of Claisen substrates were prepared and rearranged. In each case, the mono-Claisen rearrangement products (**14, 20, 26,** and **32**) were smoothly formed after 1–4 h at 60–70° in benzene. After desilylation and methylation, the yields of purified monomethyl ester acetates **15, 21, 27,** and **33** ranged from 40 to 55% (overall yield from the starting glycal). Under these conditions, only trace amounts of the tandem-Claisen products (0–3%) could be isolated after methylation. Upon prolonged heating at 60–70° (several days) or heating at higher temperatures (>100°), tandem-Claisen rearrangement products were formed in all cases (**16, 22, 28,** and **34**). As before, these products were characterized as the methyl esters **17, 23, 28,** and **35**, and the overall yields of purified compounds from the starting glycal are also indicated in the scheme of structures. The yields of tandem-Claisen rearrangement products were not optimized and, in several cases, the sluggish second rearrangement was still incomplete when the reaction was stopped.

The results demonstrate the generality of the mono-Claisen process. Substrates with different configurations and substitution patterns all rearranged smoothly. It is interesting to note that the mono-Claisen rearrangement of **30** proceeded through a tris(ketenesilyl)acetal **31** to produce the ester diacetate **33**. Overall, this is a most valuable method for the direct stereocontrolled formation of *C*-glycosyl compounds from glycal acetates without protection of the hydroxy groups.

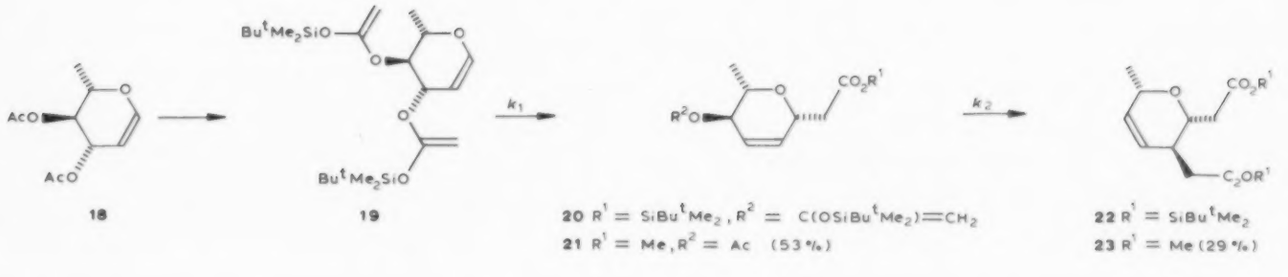
A relative-rate study of the above-described rearrangements was undertaken to ascertain the magnitude of the rate difference between the first (k_1) and second (k_2) Claisen rearrangements. Product ratios were determined by integration of appropriate resonances in the ^{1}H-n.m.r. spectra (C_6D_6), and all rates were first order over several half-lives. The results are summarized in Table I. Also collected in Table I are the rates for several model systems, derived from, cyclohexenediol (**36**), dihydropyranol (**37**), and cyclohexenol (**38**). With the important exception of



12 13

14 R^1 = $SiBu^tMe_2$, R^2 = $C(OSiBu^tMe_2)=CH_2$
15 R^1 = Me, R^2 = Ac (55%)

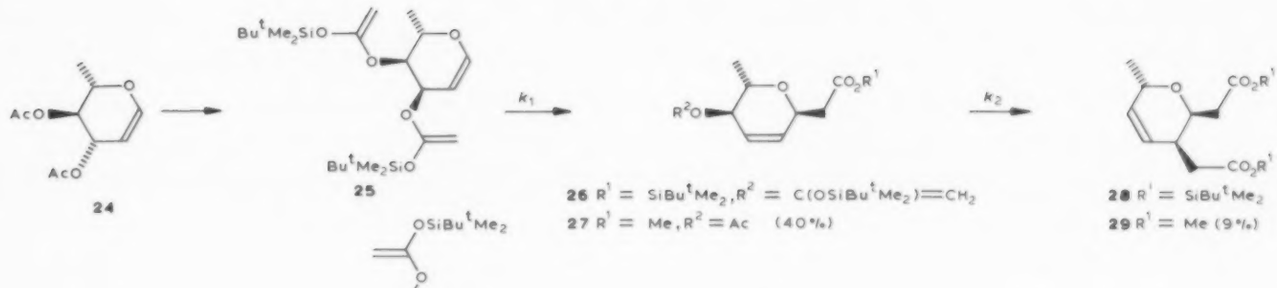
16 R^1 = $SiBu^tMe_2$
17 R^1 = Me (20%)



18 19

20 R^1 = $SiBu^tMe_2$, R^2 = $C(OSiBu^tMe_2)=CH_2$
21 R^1 = Me, R^2 = Ac (53%)

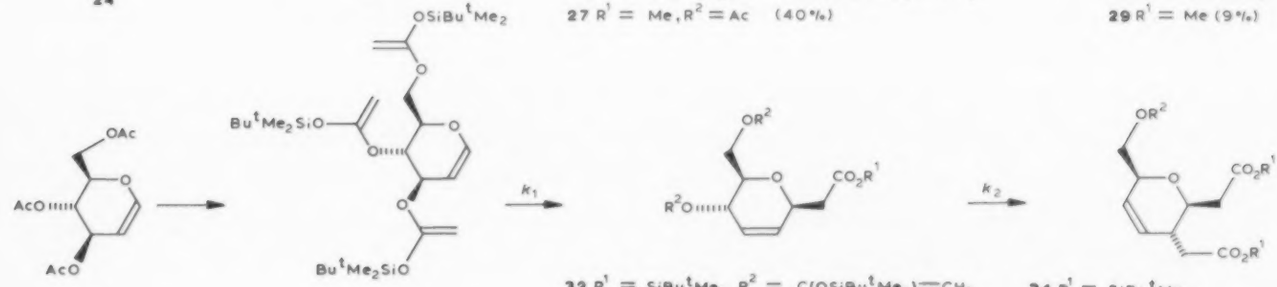
22 R^1 = $SiBu^tMe_2$
23 R^1 = Me (29%)



24 25

26 R^1 = $SiBu^tMe_2$, R^2 = $C(OSiBu^tMe_2)=CH_2$
27 R^1 = Me, R^2 = Ac (40%)

28 R^1 = $SiBu^tMe_2$
29 R^1 = Me (9%)



30 31

32 R^1 = $SiBu^tMe_2$, R^2 = $C(OSiBu^tMe_2)=CH_2$
33 R^1 = Me, R^2 = Ac (55%)

34 R^1 = $SiBu^tMe_2$,
R^2 = $C(OSiBu^tMe_2)=CH_2$
35 R^1 = Me, R^2 = Ac (13%)

TABLE I

CLAISEN RATE MEASUREMENTS OF COMPOUNDS **5, 13, 19, 25, 31, 37, 41,** AND **44**

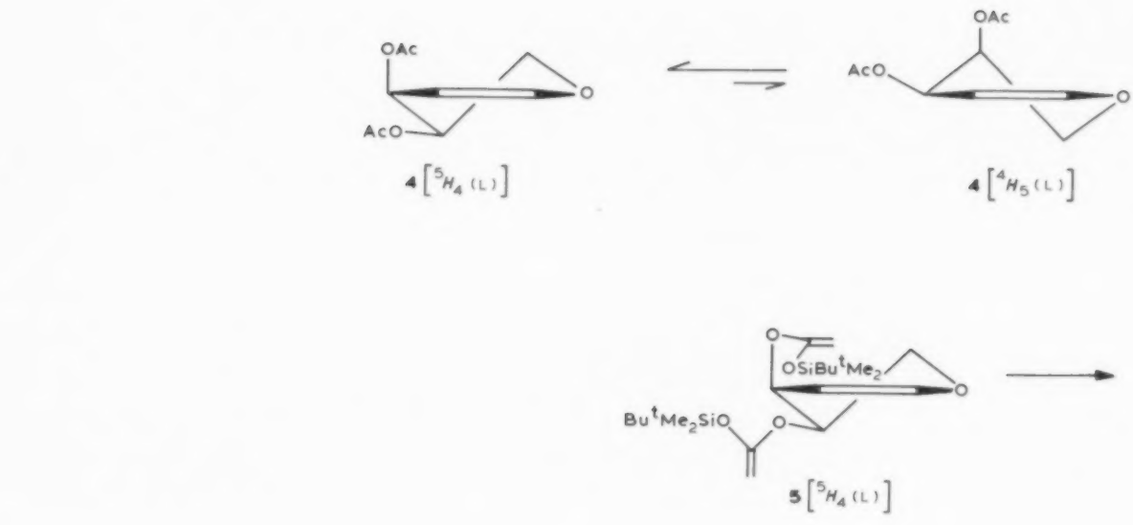
Compound	K_1 *(sec^{-1})* *(× 10^{-5})*	k_2 *(sec^{-1})* *(×10^{-6})*	*Temp. (degrees)*	k_1/k_2
5	48	25	70	20
13	68	19	60	35
19	200	3.5	60	575
25	42	8.1	60	50
31	160	7.1	60	225
37	3.3	17	65	2
41	44	[a]	60	10
44	[a]	48	60	

[a]Not applicable, see text for explanation.

the carbocyclic analog **36**, the first Claisen rearrangement is 10–575 times faster than its partner.

We have considered three possible origins for the intriguing selectivity of these apparently similar Claisen rearrangements. The origin of the general effect $k_1 > k_2$ can be (a) conformational, (b) steric, or (c) substituent-controlled (stereoelectronic). (Of course, combinations are possible.) The importance of conformational effects is readily assessed (see Scheme 4). For proper orbital overlap in the Claisen rearrangement, the ketenesilylacetal C–O bond must attain an axial-like orientation. The L-arabinal derivative **4** is known to exist preponderantly in the $^5H_4$(L) conformation, despite the fact that the alternative $^4H_5$(L) conformation has no 1,3-diaxial-like interaction[22]. The reasons for this will be addressed shortly. According to a ^{1}H-n.m.r. coupling-constant analysis, bis(ketenesilyl)acetal **5** has a conformational preference similar to **4**. Thus, the requisite C–O bond is preponderantly axial, and a conformational problem is not encountered in the Claisen transition state proceeding to **6**. While **6** must initially be formed in conformation **6a**, it rapidly flips into conformation **6b** to minimize diaxial-like interactions. The magnitude of the vicinal and allylic coupling constants[6,10,23] of H-1 and H-4 are particularly diagnostic in this and related cases (see Experimental section). Compound **6b** is now in the conformation required for rearrangement and there is no inherent bias against the transition-state conformation of second Claisen rearrangement. Thus, the basic rate difference ($k_1 > k_2$) is not explained by conformational considerations.

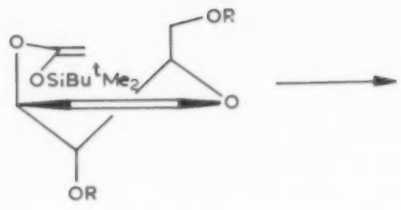
However, the importance of conformational aspects cannot be overlooked. Consider a similar analysis of the D-glucal derivative **30** (see Scheme 5) which is known to exist as a mixture of $^4H_5$(D) and $^5H_4$(D) conformers in solution. At first sight, the observation that these two conformers are comparable in energy may seem surprising. However, this will be rationalized by stereoelectronic considerations *(vide infra)*. Again, we can propose that ketenesilylacetal **31** has a similar



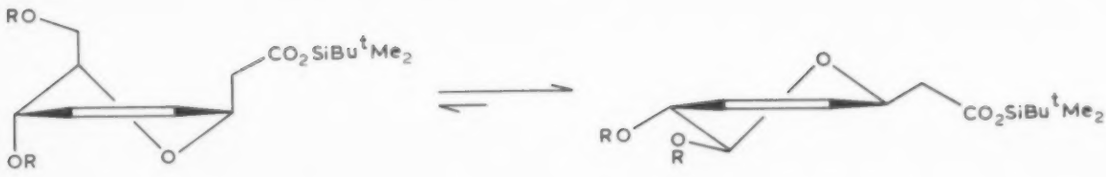
6a 6b

Scheme 4

30 $\left[{}^{5}H_{4}(D)\right]$ **30** $\left[{}^{4}H_{5}(D)\right]$



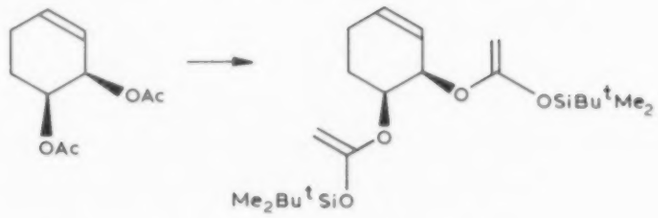
31



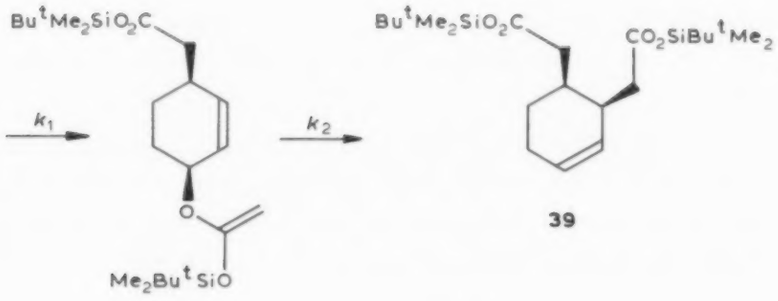
32*a* **32***e*

R = —C(OSiBu^{t}Me$_2$)=CH$_2$

Scheme 5

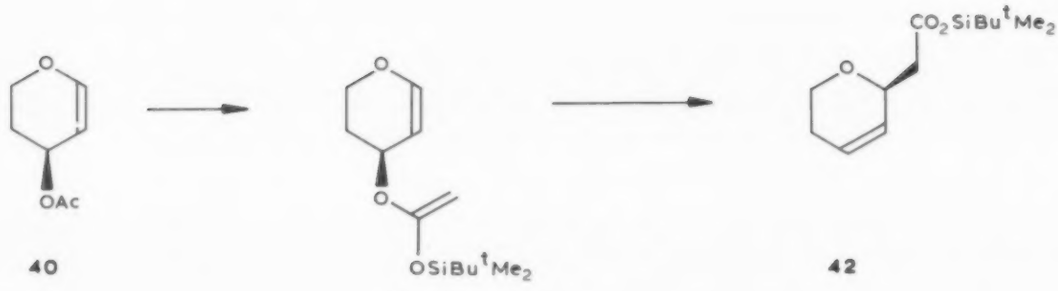


36 37

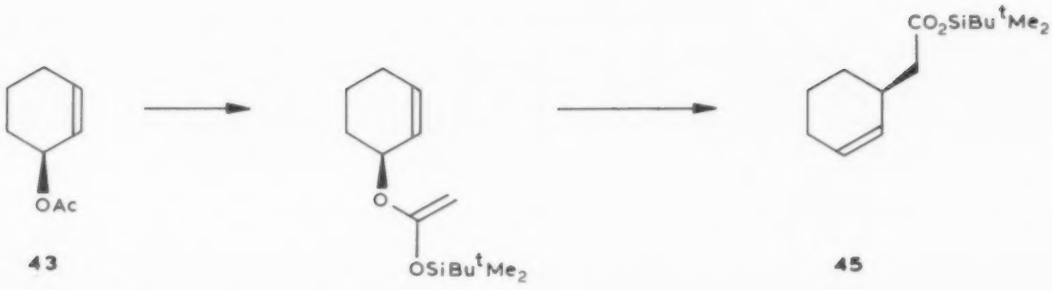


39

38



40 41 42



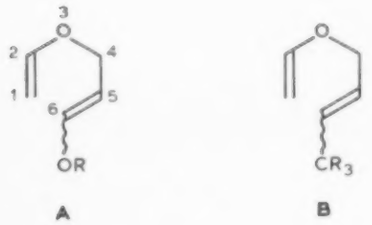
43 44 45

Scheme 6.

conformational preference to **30**. Assuming that transition-state conformational energies roughly parallel their ground-state precursors, rearrangement *via* the $^5H_4$(D) conformation of **31** should be reasonable. While the product is formed in conformation **32a**, it rapidly flips to the conformation **32e** to place all three substituents in equatorial positions. In the case of the D-glucal derivative then, there is a conformational bias against the second rearrangement according to this analysis, which correlates ground-state, conformational-energy differences to transition-state energies. While this analysis explains why the L-rhamnal and D-glucal derivatives show k_1/k_2 ratios much greater than those of the L-arabinal, D-xylal, or L-digitoxal derivatives, it is still not obvious why the underlying principle should operate. Specifically, why should **30** and **31** exist as an energetically comparable $^4H_5 \rightleftarrows {}^5H_4$(D) mixture, whereas **32** exists preferentially in the all equatorial conformation **32e**?

A steric rationale may also be put forward; perhaps the second Claisen rearrangement is more hindered than the first owing to the neighboring acetic ester side-chain. Conformational analysis (see Schemes 4 and 5) indicated that this is not likely, since the equatorially oriented CH_2CO_2R group should provide little steric hindrance to an axially entering substituent. The models outlined in Scheme 6 address this question. Assuming that this steric argument is correct, the carbocyclic analogs **37–39** might be expected to show a similar $k_1 > k_2$ preference to **5**. In fact, k_1 is only marginally greater than k_2 (Table I). In another example, the rates of rearrangement of **41** and **44** should be similar based on both steric and conformational arguments (**41** and **44** have similar conformational preferences)[24]; however, **41** rearranges at a rate one order of magnitude faster than **44** (Table I).

To summarize, the Claisen selectivity observed is not adequately explained by steric or conformational considerations. While configurations play only a minor role, conformations can be important. However, the observed conformational effects serve only to reinforce a "pre-existing" selectivity. A third obvious difference between the two Claisen rearrangements is that resulting from a substituent. The compound subject to the first Claisen rearrangement always possesses an oxygen atom in the γ-allylic position (C-6, see **A** in Scheme 7), whereas the compound subjected to the second Claisen rearrangement has a carbon atom in the

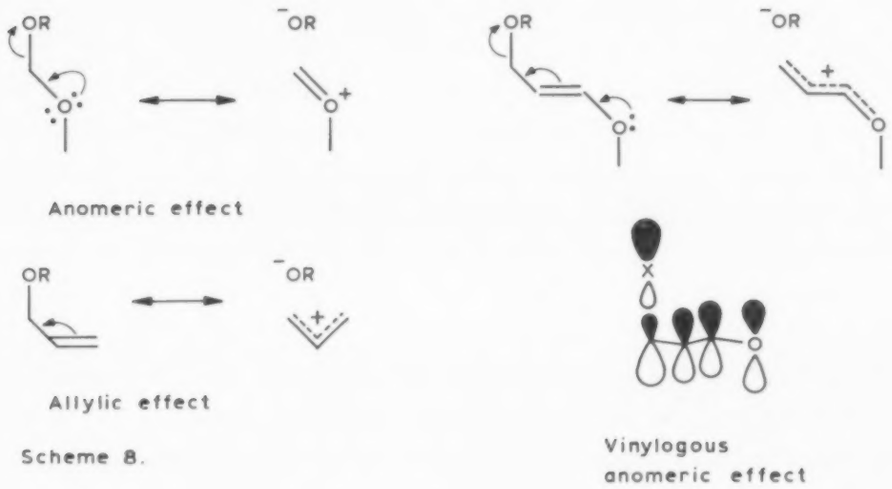


Scheme 7

*Both rearrangements are strongly accelerated by the Bu^{t}Me$_2$SiO-2 substituent[3], and studies[25] in our laboratory have shown that the effect of O-6 is independent of substitution at C-2.

same position (**B** in Scheme 7). Clearly, the first Claisen rearrangement is accelerated by a substituent effect*. Thus, an electron-donating substituent in the γ-allylic position (C-6) accelerates the Claisen rearrangement. In addition to the studies outlined herein, a variety of rearrangements in acyclic systems have confirmed the generality of this statement[6,25]. The following section will provide a stereoelectronic rationale, termed the vinylogous anomeric effect, which allowed us to interpret both the known ground-state conformational preferences of sugar glycals and the origin of the accelerating effect of the electron donating oxygen atom on the Claisen rearrangement.

The vinylogous anomeric effect. — The Carpenter model has been widely used to interpret and predict substituent effects on the Claisen rearrangement[26]. This treatment calculates the difference in Huckel π-electron energy between suitable reactant and transition-state models. In the present model, an electron-donating substituent in the γ-allylic position is predicted to be decelerating. Since the basic premise of the Carpenter model seems reasonable, an overriding effect must be operating in this particular case.



Scheme 8.

We propose that the rate accelerating effect of a γ-electron-donating substituent is stereoelectronic in nature, and we introduce a rationale based on the "vinylogous anomeric effect" (VAE)[27,*] (see Scheme 8). The "anomeric effect" is well known as a guiding stereoelectronic principle in carbohydrate chemistry for interpretation of both ground-state conformational preferences, and reactivity[28,29]. In molecular orbital terms, an $n \rightarrow \sigma^*$ interaction is invoked. Alternatively, simple resonance theory permits interpretation of the anomeric effect *via* the standard "double-bond–no-bond" resonance picture. Similarly, the "allylic effect" has also been recognized as a useful principle in carbohydrate chemistry[30]. A molecular orbital diagram for the VAE invoking $\pi \rightarrow \sigma^*$ stabilization may also be con-

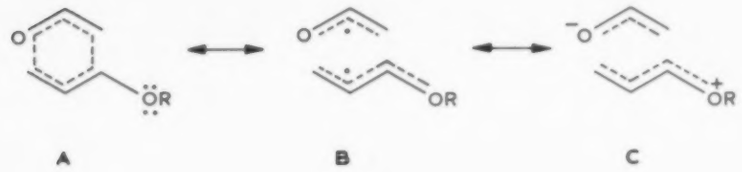
*The term "vinylogous anomeric effect" has been independently introduced, see ref. 27.

structed[31]. The simple resonance picture is also useful for the present discussion. All three "effects" are obviously related and each may be considered as an example of a more fundamental stereoelectronic principle[29]. Since an enol ether has a higher lying π-orbital (*i.e.*, better donor) than a simple olefin, the VAE should be of larger magnitude than the allylic effect[31].

Drawing an analogy of the anomeric and allylic effects, the VAE may be expected to have both conformational and chemical consequences[28,29]. From a conformational standpoint, an axial-like preference for a vinylogously anomeric C–X bond may be expected in order to provide optimum geometry for orbital interaction. Spectroscopic evidence is in good accord with this proposal and such conformational preferences have been previously recognized[22,24,27,32]. As an illustrative example, consider the ground state conformational preferences of **4** (Scheme 4) and **30** (Scheme 5). According to ^{1}H-n.m.r. coupling-constant analysis, **4** prefers the $^5H_4$(L) conformation (having the vinylogously anomeric C-4–O bond axial-like and the C-5–O bond equatorial-like) over the $^4H_5$(L) conformation (which reverses the configuration of these two substituents). While such a conformational preference may be attributed to $A_{1,2}$ strain or decreased 1,3-diaxial-like interactions in dihydropyrans relative to pyrans, we feel that the VAE is likely the most important reason. While **30** has been shown to exist in the $^4H_5$(D) conformation in the solid state[33], the ^{1}H-n.m.r. spectrum for a solution is more consistent with an ~3:2 mixture of the $^4H_5$ and $^5H_4$(D) conformers. The energetic viability of the "all axial-like" $^5H_4$(D) conformer may again be attributed to the vinylogous anomeric effect. Indeed, all cationic reactions of **30**, such as the Ferrier rearrangement[34], must proceed *via* the $^5H_4$(D) conformation. The VAE principle is readily extended to interpret conformational preferences of other glycals and related enol ethers in solution[22,24,27,32].

We turn now to the chemical consequences of the VAE. At first glance, a γ-allylic oxygen atom should retard the Claisen rearrangement, since the VAE predicts a reduction in ground-state energy relative to an unsubstituted analog. This is not the case. Since the VAE is expected to stabilize the transition state more than the ground state, a net acceleration is anticipated.

Based on elegant isotope effect studies, Gajewski and Conrad[35], and McMichael and Korver[36] have concluded that the aliphatic Claisen rearrangement has a transition state with a bond-breaking well advanced with respect to bond-making. Substituents that will facilitate bond-breaking by any means can then be expected to accelerate the Claisen rearrangement. According to the VAE, the C-3–O-4 bond is weakened relative to an unsubstituted counterpart, and its cleavage is stabilized in the transition state by the donation of electron density. Scheme 9 presents a resonance picture of the transition state which emphasizes the importance of bond-breaking. This VAE bond-breaking interpretation stresses the importance of the dipolar resonance contributor (**C**) in this Claisen rearrangement and indeed predicts that a significant, substituent-induced solvent effect may be observed. Recently, we[25], and Carpenter *et al.*[37] have observed unprecedented solvent accelera-



A B C

Scheme 9.

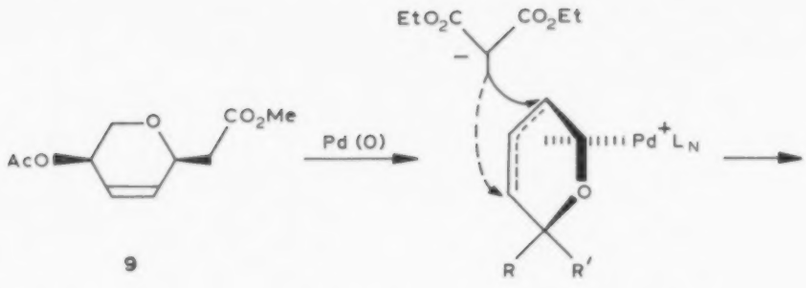
tions of related Claisen rearrangements. Note then that, in line with the anomeric effect, the VAE may impart molecules with both an increased stability and increased reactivity. Furthermore, this kinetic accelerating effect of the VAE can be compared to the kinetic anomeric effect[28] which is usually invoked for stepwise, ionic reactions. There is no reason why such effects should not operate in concerted, nonsynchronous, pericyclic reactions such as the Claisen rearrangement.

Finally, the VAE provides an explanation for the differences in relative rates (k_1/k_2) between the D-glucal **31** and the L-arabinal **5** experiments. In the first case, a much larger k_1/k_2 ratio was observed. While a 1,3-diaxial-like interaction is present in both the ground and transition state of **31**, this is largely offset by the VAE. However, the second Claisen rearrangement does not benefit from the VAE and **32** suffers 1,3-diaxial-like interactions in both the ground and transition states. Thus, the transition-state energy of the second Claisen rearrangement is raised further relative to the first.

Pseudomonic acid intermediates. — The controlled mono-Claisen rearrangement of **4** provides a direct method for introduction of the *C*-glycosyl chain of the pseudomonic acids. The remaining allylic acetate group must then serve as a handle for selective introduction of the second side-chain. Net retention of both regio- and stereo-selectivity of the allylic acetate **9** is required and, based on mechanistic considerations, a palladium-catalyzed nucleophilic displacement appeared to provide an ideal solution[38]. Such reactions with stabilized carbon-nucleophiles are well known to occur with retention of configuration *via* a double-inversion mechanism. On the other hand, regioselectivity is not determined by the precursor allylic acetate group but by steric or electronic biases (or both) in the intermediate π-allyl palladium complex.

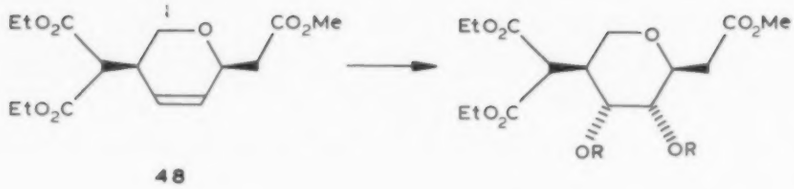
Addition of diethyl sodiomalonate to acetate **9** catalyzed by $Pd(dppe)_2$ provided essentially a single product which was readily identified as **48**. The high degree of regiocontrol may be reasonably explained by approach of the malonate reagent to the allylic position remote from the existing side-chain in the intermediate π-allyl palladium complex **46**. Catalytic osmylation[39] provided a single *cis*-diol **49** with the proper functional-group disposition for pseudomonic acid C. This diol was fully characterized by formation of both diacetate **50** and dibenzoate **51** derivatives.

The Pd(0) catalyzed displacement proved quite general. The related acetate compound **27** gave **52** as the sole isolated product in high yield. On the other hand, the D-xylal derivative **15** provided a 2:1 mixture of the regioisomers **53** and **54**. In



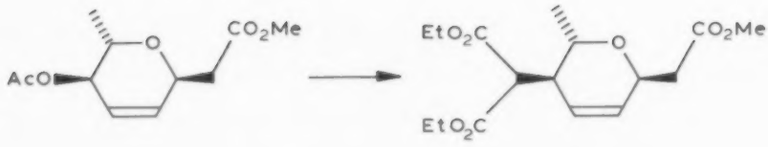
9

46 R = CH_2CO_2Me, R' = H
47 R = H, R' = CH_2CO_2Me

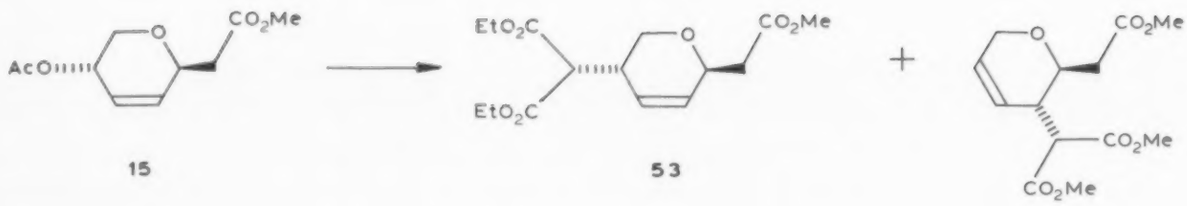


48

49 R = H
50 R = Ac
51 R = Bz



27 52

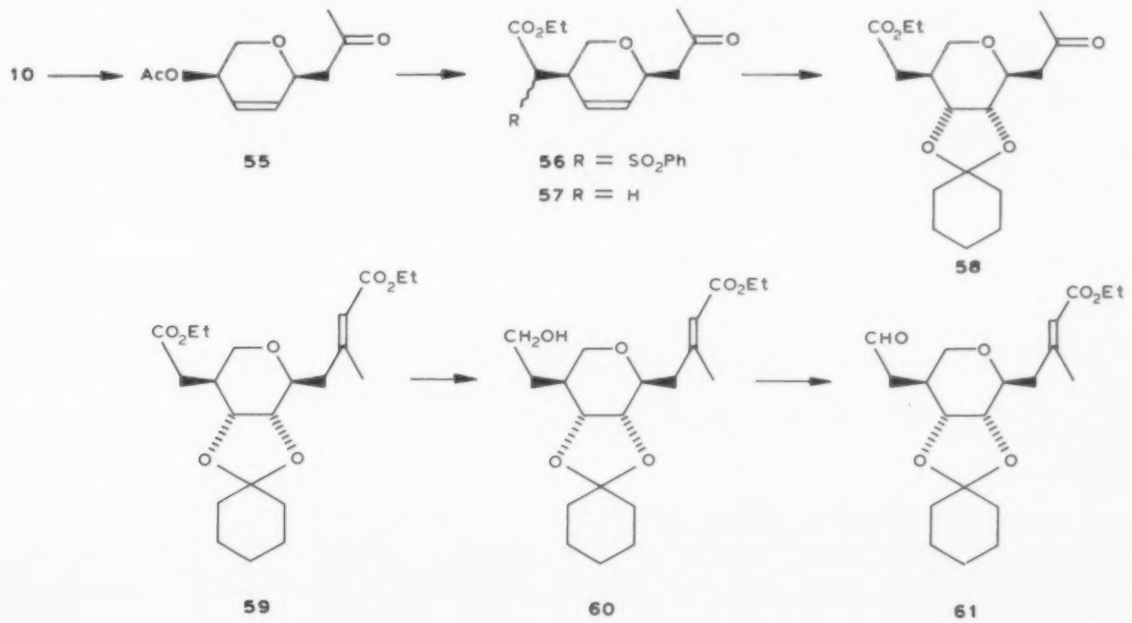


15 53 54

this case, the pendant C-2 side-chain is in position *cis* to the metal in the intermediate π-allyl palladium complex **47** and is not in a position to control the approach of an incoming nucleophile. The aforementioned regiochemical preferences are in full accord with previous observations in Pd(0)-catalyzed displacements of carbohydrate-derived allylic acetate compounds[40].

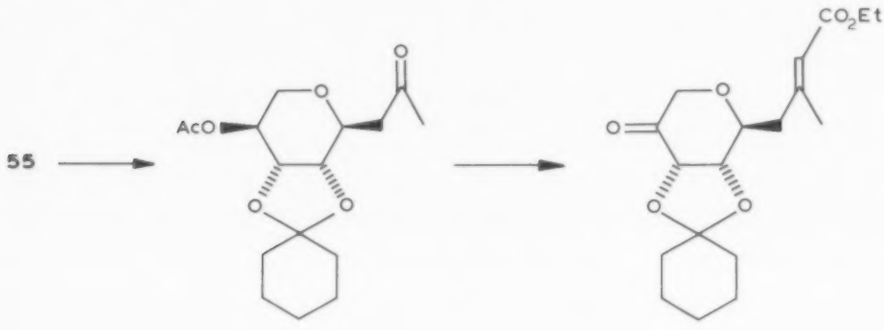
To complete the approach to pseudomonic acid C, a suitable function group differentiation was then required. Unstable acid **10** was converted directly into the methyl ketone **55** *via* a reaction of the derived acid chloride with lithium dimethyl cuprate. Alternatively, a mixed-anhydride method was also employed[41]. Palladium(0) catalyzed coupling of **55** with ethyl phenylsulfonylacetate provided **56** as a 1:1 mixture of diastereomers. Direct sodium amalgam reduction[42] of the mixture provided a single product **57** in high yield. The use of the more acidic additive sodium dihydrogenphosphate rather than the standard disodiumhydrogen phosphate was essential in this reductive desulfonylation to prevent base-catalytic side reactions, including hydrolysis and transesterification. Standard catalyzed osmylation and protection of the resultant diol as the cyclohexylidene acetal provided the ketoester **58**. After standard olefination, the *E*-olefin **59** was isolated as the major product, along with the corresponding *Z* isomer (3:1 ratio).

Finally, the two esters present in **59** were differentiated by reduction. Treatment of **59** with *in situ* generated lithium butyl(diisobutyl)aluminum hydride complex[43] (1.2 equiv.) provided a 1:1 mixture of **60** and **61** along with a small proportion of recovered **59**; it should be noted that both products resulted from the reduction of the saturated ethyl ester. Related selective reductions of saturated ketones in the presence of unsaturated ketones have previously been reported[44]. Alcohol **60** and aldehyde **61** were readily separable, and **60** was readily oxidized to **61**. Aldehyde **61** is a key intermediate in both the original Kozikowski *et al.*[8] (racemic) and Fleet *et al.*[13] (optically active) syntheses of pseudomonic acid C, and spectra



obtained from **61** compared favorably with authentic spectra kindly provided by the aforementioned authors.

For completion of the synthesis of **1**, a short sequence of olefination, ester interchange, and deprotection was required. In comparison to other syntheses, this approach is most direct and efficient. Only nine steps were required for the conversion of **4** into the highly functionalized aldehyde **61**, which means that a twelve-step, formal, total synthesis of pseudomonic acid C is at hand. Although we have not investigated further modifications, further abbreviation of the sequence of reactions is possible. Ester interchange may be omitted by use of the appropriate phosphonate in the olefination reaction[14,15], and use of a more functionalized intermediate in the palladium(0)-catalyzed alkylation might provide a more convergent approach to side-chain introduction. The latter modification might indeed be attractive owing to problems inherent[8,12–15] in the olefination of **61**. Finally, a highly functionalized intermediate **63** for the synthesis of pseudomonic acid A analogs is readily available from **55**. Hydroxylation and protection of **55** provided **62**. Subsequent olefination, acetate cleavage, and oxidation gave[16] **63** in short order.



62 63

In conclusion, the mono-Claisen rearrangement of carbohydrate glycals provides a facile and selective access to functionalized C-glycosyl compounds. When coupled with Pd(0)-catalyzed allylic alkylation, it results in a versatile route to the pseudomonic acid class of antibiotics. Perhaps more importantly, consideration of the selectivity observed in the sequential Claisen rearrangements has led to the introduction of the general principle of the vinylogous anomeric effect. It is expected that this principle will prove useful in the prediction and understanding of both the conformations and reactivity of carbohydrate glycals and related compounds.

EXPERIMENTAL

General methods. — Melting points and boiling points are uncorrected. Reported temperatures for Kugelrohr distillation refer to the temperature of the oven and are not true boiling points. Analytical t.l.c. was performed on Merck Silica Gel 60 F-254. Flash and medium-pressure column chromatography was performed on

Silica Gel 60 (230–400 mesh, ASTM). Preparative chromatography was also performed on a Waters Prep LC/system 500A HPLC using Prep PAK-500 silica gel cartridges. All reactions were performed under an N_2 atmosphere unless otherwise indicated. Oxolane, ethylene glycol dimethyl ether (DME), diethyl ether, and benzene were distilled from Na and benzophenone immediately before use. *N,N,N′,N′,N″,N″*-Hexamethylphosphoramide (HMPA), diisopropylamine, triethylamine, acetonitrile, and dichloromethane were distilled from CaH_2.

cis-[*(3,4-Dihydro-2*H*-pyran-3,4-diyl)bis(oxyethenylideneoxy)*]*bis*[*1,1-dimethylethyl)dimethylsilane*]. (**5**). — A stirred solution of diisopropylamine (925 μL, 6.6 mmol) in oxolane (4 mL) was cooled to 0° and treated with butyllithium (3.7 mL, 6.3 mmol, 1.7M in hexane) over several minutes. After being stirred for 10 min, the solution was cooled to −78° and 1,5-anhydro-2-deoxy-L-*erythro*-pent-1-enitol[19] (**4**) (600 mg, 3.0 mmol) in oxolane (4 mL) was added dropwise over 2–3 min. After 15 min, *tert*-butylchlorodimethylsilane (995 mg, 6.6 mmol) in HMPA (4 mL) was added. The resulting solution was stirred for an additional 1.5 h and poured into cold water–pentane. The pentane extract was washed with cold water and NaCl solutions, and dried ($MgSO_4$). Evaporation under reduced pressure gave **5** (1.28 g, 100%), yellow viscous liquid; ^{1}H-n.m.r. (C_6D_6): δ 6.15 (d, 1 H, *J* 6 Hz, H-2), 4.83 (dd, 1 H, *J* 6, 4 Hz, H-3), 4.43 (m, 1 H, H-4), 4.17 (dt, 1 H, *J* 9, 4 Hz, H-5), 4.08 (t, 1 H, *J* 9 Hz, H-6*a*), 3.83 (ddd, 1 H, *J* 9, 4, and 1 Hz, H-6*e*), 3.56 (d, 1 H, *J* 4 Hz, $=CH_2$), 3.50 (d, 1 H, *J* 4 Hz, $=CH_2$), 3.27 (d, 1 H, *J* 4 Hz, $=CH_2$), 3.32 (d, 1 H, *J* 4 Hz, $=CH_2$), 0.98 (s, 9 H, SiC_4H_9), 0.96 (s, 9 H, SiC_4H_9), 0.27 (s, 3 H, $SiCH_3$), 0.25 (s, 3 H, $SiCH_3$), 0.23 (s, 3 H, $SiCH_3$), and 0.21 (s, 3 H, $SiCH_3$).

*Methyl (2*R-cis*)-5-acetoxy-5,6-dihydro-2*H*-pyran-2-acetate* (**9**). — Ketenesilyl acetal **5** (531 mg, 1.24 mmol) was dissolved in chloroform (3 mL) and stirred for 6 h at 60°. After concentration, the residue was dissolved in HMPA (2 mL) and stirred for 12 h with water (130 μL, 7.4 mmol), KF (432 mg, 7.4 mmol), and $KHCO_3$ (745 mg, 7.4 mmol). Methyl iodide (1.23 mL) was added and the mixture stirred for an additional 12 h. Extraction with ether, followed by chromatography (1:3 ethyl acetate–hexane) afforded **9** (130 mg, 49%), clear oil; $[\alpha]_D^{25}$ −146° (*c* 0.92, chloroform); $\nu_{max}^{CHCl_3}$ 3000, 1730, 1430, 1370, 1200, 1040, and 740 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 6.02 (m, 2 H, H-3,4), 5.00 (m, 1 H, H-5), 4.49 (m, 1 H, H-2), 4.06 (d, 1 H, *J* 12 Hz, H-6*e*), 3.80 (dd, 1 H, *J* 12, 4 Hz, H-6*a*), 3.74 (s, 3 H, OCH_3), 2.68 (dd, 1 H, *J* 15, 7 Hz, CH_2CO_2), 2.55 (dd, 1 H, *J* 15, 5 Hz, CH_2CO_2), and 2.11 (s, 3 H, $OCOCH_3$); m.s.: *m/z* 196, 184, 154, 142, and 141.

Anal. Calc. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.94; H, 6.40.

*(2*R-cis*)-5-Acetoxy-5,6-dihydro-2*H*-pyran-2-acetic acid* (**10**). — Compound **4** (2.21 g, 11.0 mmol) was converted into the bis(ketenesilyl)acetal **5** as described above. This was dissolved in chloroform (40 mL) and stirred for 6 h at 60°. After evaporation of the chloroform solution, the residue was dissolved in acetonitrile (20 mL), and KF (3.84 g, 66 mmol), water (1.2 mL, 66 mmol), and $KHCO_3$ (6.61 g, 66 mmol) were added. The mixture was stirred for 15 h at 25° and poured into water (150 mL). The aqueous solution was washed with ether, acidified to pH 3

with 6M HCl saturated with NaCl, and extracted with ethyl acetate. The extract was washed with NaCl solution, dried ($MgSO_4$), and evaporated to give **10** (1.41 g, 64.2%), thick oil, which was used for the next step without further purification. It crystallized upon standing, m.p. 68–70°; $\nu_{max}^{CHCl_3}$ 3600–2300, 1710, 1370, 1200, 1080, 1040, 960, and 710 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 6.02 (br. s, 2 H, H-2,3), 5.02 (br. s, 1 H, H-2), 4.47 (m, 1 H, H-5), 4.10 (d, 1 H, *J* 12.9 Hz, H-6*e*), 3.82 (dd, 1 H, *J* 12.9, 2.8 Hz, H-6*a*), 2.71 (dd, 1 H, *J* 16, 8.3 Hz, CH_2CO_2), and 2.63 (dd, 1 H, *J* 16, 5.7 Hz, CH_2CO_2).

(1S,6S)2,7-Dioxabicyclo[4,3,5]non-4-en-8-one[11] (**8**). — Acid **10** (980 mg, 4.89 mmol) resolidified after being kept for three days at 25°. Flash-column chromatography of the resulting black solid on silica gel with 1:1 ethyl acetate–hexane afforded **8** (200 mg, 43.9%), white crystalline solid; m.p. 88–90°; $\nu_{max}^{CHCl_3}$ 3020, 1770, 1340, 1260–1160, 1100, 1050, 990, and 720 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 6.28 (ddq, 1 H, *J* 11.5, 4.60, 1.1 Hz, H-5), 6.10 (m, 1 H, H-4), 4.56 (m, 1 H, H-3), 4.28 (dd, 1 H, *J* 4.6, 3.5 Hz, H-6*a*), 4.22 (ddd, 1 H, *J* 18.4, 4.6, 2.3 Hz, H-6*b*), 4.1 (ddd, 1 H, *J* 18.4, 4.6, 2.3 Hz, H-6*a*), 2.84 (dd, 1 H, *J* 18.4, 4.6 Hz, H-7*a*), and 2.64 (d, 1 H, *J* 18.4 Hz, H-7*b*); m.s. *m/z* 140 (M^+), 96, 84, and 70; lit.[11] (racemic) m.p. 71–72°.

*Dimethyl (5*R-cis*)-5,6-dihydro-2*H*-pyran-5,6-bisacetate* (**11**). — Compound **5** was heated at reflux in toluene (16 h), and then methylated as described for **9**. Purification by flash chromatography (1:4 ethyl acetate–hexane) gave **11**; $\nu_{max}^{CHCl_3}$ 3000, 2900, 1720, 1440, 1300–1160, 1080, and 990 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.92–5.83 (m, 1 H, H-5), 5.73 (br. d, 1 H, *J* 12 Hz, H-4), 4.25–4.11 (m, 3 H, H-2,6*e*,6*a*), 3.71 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3, and 2.62–2.31 (m, 5 H, 2 CH_2CO_2, H-2); m.s.: *m/z* 228 (M^+), 196, 169, 154, 108, and 98; m.s. calc. for $C_{11}H_{16}O_5$, 228.0998; found, 228.0990.

Anal. Calc. for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 58.01; H, 7.02.

*3,4-Di-O-acetyl-1,5-anhydro-2,6-dideoxy-*L-ribo*-1-enitol* (**24**). — To a stirred solution of 1,5-anhydro-2,6-dideoxy-L-*arabino*-hex-1-enitol[45] (**18**; 1.42 g, 10.9 mmol) in chloroform (25 mL) was added MnO_2 (10.9 g). After stirring for 36 h at 25°, the mixture was filtered and the filter cake washed with chloroform. Concentration of the organic layer, followed by flash-column chromatography (2:1 ethyl acetate–hexane) gave 1,5-anhydro-2,6-dideoxy-L-*erythro*-hex-1-en-3-ulose[45] (807 mg, 58%), white crystals, m.p. 92.5–93°, lit.[45] (for enantiomer) 87°; ^{1}H-n.m.r. ($CDCl_3$): δ 7.38 (d, 1 H, *J* 5.7 Hz), 5.45 (d, 1 H, *J* 5.7 Hz), 4.19 (m, 1 H), 3.96 (dd, 1 H, *J* 12.9, 1.8 Hz), 3.5 (d, 1 H, *J* 1.8 Hz), and 1.57 (d, 3 H, *J* 6.0 Hz).

To a warmed solution of lithium tri(*tert*-butoxy)aluminium hydride (45.4 mg, 0.18 mmol) in oxolane at 60° was added the aforementioned enone (17.6 mg, 0.14 mmol) in oxolane (1 mL). The mixture was heated for 2 h, cooled, and extracted with ether, followed by concentration of the ethereal solution to give 1,5-anhydro-2,6-dideoxy-L-*ribo*-1-enitol (13.6 mg) as a yellow liquid. Flash column chromatography of the residue (1:2 ethyl acetate–hexane) afforded the pure diol (6.2 mg, 34%), white solid, m.p. 116°, lit.[46] (for enantiomer) m.p. 115.3°, $[\alpha]_D^{25}$ −335° (*c* 0.185, methanol), lit.[46] (for enantiomer) +314° (*c* 1.03, methanol); ^{1}H-n.m.r. ($CDCl_3$): δ 6.43 (d, 1 H, *J* 5.9 Hz), 4.95 (t, 1 H, *J* 5.4 Hz), 4.09 (m, 1 H), 3.80 (m,

1 H), 3.48 (td, 1 H, *J* 9.3, 4.3 Hz), 2.53 (d, 1 H, *J* 9.3 Hz), 1.79 (d, 1 H, *J* 6.1 Hz), and 1.39 (d, 3 H, *J* 3.6 Hz).

Standard acetylation with acetic anhydride and pyridine of the just described compound (14.8 mg, 0.11 mmol) gave **24** (23.1 mg, 98%), white crystals, m.p. 52–53°, lit.[47] (for enantiomer) m.p. 51.5°; ^{1}H-n.m.r. ($CDCl_3$): δ 6.49 (d, 1 H, *J* 5.9 Hz), 5.40 (dd, 1 H, *J* 5.7, 4.0 Hz), 4.86 (m, 2 H), 4.17 (m, 1 H), 2.07 (s, 3 H), 2.05 (s, 3 H), and 1.29 (d, 3 H, *J* 6.3 Hz).

Standard preparation of ketenesilyl acetals from acetates. — trans-[*(3,4-Dihydro-2*H*-pyran-3,4-diyl)bis(oxyethenylideneoxy)]bis[(1,1-dimethylethyl)dimethylsilane*] (**13**). A solution of diisopropylamine (1.6 mL, 11.6 mmol) in oxolane (20 mL) was cooled to 0° and treated with butyllithium (6.9 mL, 11.1 mmol, 1.6M in hexane) over several min. After the mixture had been stirred for an additional 10 min, it was cooled to −78° and a mixture of 3,4-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*threo*-pent-1-enitol[47] (**12**) (1.06 g, 5.29 mmol) and *tert*-butylchlorodimethylsilane (1.75 g, 11.6 mmol) in HMPA (10 mL) was added. Completion of this experiment as described for **4** gave **13** (2.17 g, 95.7%), clear oil; ^{1}H-n.m.r. ($CDCl_3$): δ 6.33 (d, 1 H, *J* 7 Hz), 4.9–4.85 (m, 1 H), 4.52–4.46 (m, 1 H), 4.22 (m, 1 H), 4.03 (m, 1 H), 3.80 (m, 1 H), 3.56 (d, 1 H, *J* 2.5 Hz), 3.54 (d, 1 H, *J* 2.5 Hz), 3.40 (d, 1 H, *J* 4 Hz), 3.30 (d, 1 H, *J* 4 Hz), 0.97 (s, 9 H), 0.96 (s, 9 H), 0.17 (s, 6 H), and 0.15 (s, 6 H).

General Claisen rearrangement of ketenesilyl acetals (^{1}H-n.m.r. study). — Ketenesilyl acetal (~10 mg; 0.5 mL) in an appropriate solvent (C_6D_6 or $CDCl_3$) was placed in an n.m.r. tube under N_2 and then heated in an oil bath at the desired temperature. After an appropriate time-period, the solution was cooled to room temperature. The regions of peaks typical of ketenesilyl acetals and silyl esters (rearranged product) were scanned by ^{1}H-n.m.r. spectroscopy and integrated.

*Methyl (2*R*,5*S*)-5-acetoxy-5,6-dihydro-2*H*-pyran-2-acetate* (**15**). — Ketenesilyl acetal **13** was heated for 1 h at 65°, followed by standard methylation as described above, to give **15** (59%), clear oil, $[\alpha]_D^{25}$ +114° (*c* 1.22, chloroform); $\nu_{max}^{CHCl_3}$ 3000, 1750, 1430, 1360, 1200, 1160, 1090, 1040, 990, 950, 920, and 710 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.95 (m, 2 H, H-3,4), 5.21 (m, 1 H, H-5), 4.61 (m, 1 H, H-2), 4.07 (dd, 1 H, *J* 11.7, 4.9 Hz, H-6), 3.71 (s, 3 H, OCH_3), 3.58 (dd, 1 H, *J* 11.7, 6.2 Hz, H-6), 2.60 (dd, 1 H, *J* 15.4, 8.4 Hz, CH_2CO_2), 2.48 (dd, 1 H, *J* 15.4, 5.6 Hz, CH_2CO_2), and 2.06 (s, 3 H, $COCH_3$); m.s.: *m/z* 184, 154, and 141; m.s. calc. for $C_9H_{12}O_4$ (M − CH_2O), 184.0736; found, 184.0736.

*Dimethyl (5*S*,6*R*)-5,6-dihydro-2*H*-pyran-5,6-bisacetate* (**17**). — Prepared in benzene for 2 days at 65° (yield 20%), $[\alpha]_D^{25}$ −107° (*c* 0.275, chloroform); $\nu_{max}^{CHCl_3}$ 2950, 2840, 1730, 1440, 1360, 1280–1200, 1160, 1120, 1080, and 1020 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.78 (dq, 1 H, *J* 10.3, 2.2 Hz, H-4 or -5), 5.70 (dq, 1 H, *J* 10.3, 2.5 Hz, H-4 or -5), 4.14 (m, 2 H, H-6*a*,6*e*), 3.83 (q, 1 H, *J* 7 Hz, H-2), 3.71 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 2.58 (d, 2 H, *J* 6.5 Hz, CH_2CO_2), 2.56 (m, 1 H, H-3), 2.44 (dd, 1 H, *J* 15.5, 5.6 Hz, CH_2CO_2), and 2.27 (dd, 1 H, *J* 15.5, 8.3 Hz, CH_2CO_2); m.s. calc. for $C_{11}H_{16}O_5$, 228.0998; found, 228.0998.

Methyl (2S,5R,6S)-5-acetoxy-6-methyl-5,6-anhydro-2H-pyran-2-acetate (**21**). — Prepared in benzene for 1 h at 60° (yield 53%), $[\alpha]_D^{25}$ −136.5° (*c* 1.085, chloroform); $\nu_{max}^{CHCl_3}$ 2930, 2800, 1730, 1430, 1370, 1275, 1200, 1130, 1100, 1070, 1040, 1020, and 920 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.82 (dt, 1 H, *J* 10.3, 1.4 Hz, H-3), 5.72 (dt, 1 H, *J* 10.3, 1.8 Hz, H-4), 5.02 (m, 1 H, H-5), 4.57 (m, 1 H, H-2), 3.62 (s, 3 H, OCH_3), 3.62 (m, 1 H, H-6), 2.57 (dd, 1 H, *J* 15.5, 7.6 Hz, CH_2CO_2), 2.46 (dd, 1 H, *J* 15.6, 6.3 Hz, CH_2CO_2), 2.07 (s, 3 H, $OCOCH_3$), and 1.22 (d, 3 H, *J* 6.1 Hz, CH_3).

Anal. Calc. for $C_{11}H_{16}O_5$: C, 57.89; H, 7.07. Found: C, 57.65; H, 7.13.

Dimethyl (2S,5R,6S)-2-methyl-5,6-dihydro-2H-pyran-5,6-bisacetate (**23**). — Prepared in benzene for 6 days at 60° (yield 29%), $[\alpha]_D^{25}$ +107.5° (*c* 0.73, chloroform); $\nu_{max}^{CHCl_3}$ 3000, 2950, 1740, 1430, 1200, 1160, 1150, and 990 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.65 (m, 1 H, H-4 or -5), 5.62 (m, 1 H, H-4 or -5), 4.21 (m, 1 H, H-6), 3.75 (dd, 1 H, *J* 8.0, 3.5 Hz, H-2), 3.70 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 2.59 (dd, 1 H, *J* 15.5, 3.5 Hz, CH_2CO_2), 2.55 (m, 1 H, H-3), 2.50 (dd, 1 H, *J* 11.5, 8.7 Hz, CH_2CO_2), 2.36 (dd, 1 H, *J* 15.6, 4.7 Hz, CH_2CO_2), 2.16 (dd, 1 H, *J* 15.6, 9.1 Hz, CH_2CO_2), and 1.18 (d, 3 H, *J* 6.8 Hz, CH_3).

Anal. Calc. for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.29; H, 7.29.

Methyl (2R,5R,6S)-5-acetoxy-6-methyl-5,6-dihydro-2H-pyran-2-acetate (**27**). — Prepared in benzene for 2 h at 60° (yield 40%), $[\alpha]_D^{25}$ −127.5° (*c* 0.765, chloroform); $\nu_{max}^{CHCl_3}$ 3000, 1740, 1650, 1380, 1240, 1110, 1080, 1020, 930, and 900 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.93 (br. d, 1 H, *J* 10.3 Hz, H-3 or -4), 5.81 (br. d, 1 H, *J* 10.3 Hz, H-3 or -4), 4.90 (s, 1 H, H-5), 4.64 (m, 1 H, H-2), 3.87 (m, 1 H, H-6), 3.72 (s, 3 H, OCH_3), 2.70 (dd, 1 H, *J* 15.3, 8.4 Hz, CH_2CO_2), 2.53 (dd, 1 H, *J* 15.3, 5.7 Hz, CH_2CO_2), 2.08 (s, 3 H, $OCOCH_3$), and 1.23 (d, 3 H, *J* 6.5 Hz, CH_3); m.s. calc. for $C_9H_{12}O_4$ (M − CH_3CHO), 184.0736; found, 184.0736.

Dimethyl (2R,5R,6S)-2-methyl-5,6-dihydro-2H-pyran-5,6-bisacetate (**29**). — Prepared in benzene for 48 h at 60° (yield 9%), $[\alpha]_D^{25}$ +220° (*c* 0.13, chloroform); $\nu_{max}^{CHCl_3}$ 2950, 1730, 1440, 1370, 1300–1160, 1050, and 1000 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.83 (ddd, 1 H, *J* 10.1, 5.2, 2.2 Hz, H-4 or -5), 5.69 (dd, 1 H, *J* 10.3, 2.5 Hz, H-5 or -4), 4.33–4.28 (m, 2 H, H-2,6), 3.70 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 2.56–2.45 (m, 2 H, H-3, CH_2CO_2), 2.43 (dd, 1 H, *J* 6.0, 3.6 Hz, CH_2CO_2), 2.40 (dd, 1 H, *J* 12.8, 2.0 Hz, CH_2CO_2), 2.30 (dd, 1 H, *J* 15.4, 8.3 Hz, CH_2CO_2), and 1.22 (d, 3 H, *J* 6.9 Hz, CH_3); m.s. calc. for $C_{12}H_{18}O_5$, 242.1154; found, 242.1155.

Methyl (2R,5S,6R)-5-acetoxy-6-(acetyloxymethyl)-5,6-dihydro-2H-pyran-2-acetate (**33**). — Prepared in benzene for 1.5 h at 60° (yield 55%), $[\alpha]_D^{25}$ +113° (*c* 0.75, chloroform); $\nu_{max}^{CHCl_3}$ 3000, 1740, 1470, 1390, 1230, 1150, and 1080 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.88 (d, 1 H, *J* 10.3 Hz, H-3 or -4), 5.76 (d, 1 H, *J* 10.3 Hz, H-3,4), 5.26 (dm, 1 H, *J* 7.8 Hz, H-5), 4.62 (m, 1 H, H-2), 4.18 (m, 2 H, CH_2OAc), 3.72 (m, 1 H, H-6), 3.70 (s, 3 H, OCH_3), 2.63 (dd, 1 H, *J* 15.5, 7.0 Hz, CH_2CO_2), 2.48 (dd, 1 H, *J* 15.57 Hz, CH_2CO_2), 2.08 (s, 3 H, $OCOCH_3$), and 2.07 (s, 3 H, $OCOCH_3$); m.s.: *m/z* 226, 213, 184, and 142; m.s. calc. for $C_{11}H_{14}O_5$ (M − AcOH), 226.0841; found, 226,0841.

Anal. Calc. for $C_{13}H_{16}O_5$: C, 54.45; H, 6.34. Found: C, 54.26; H, 6.23.

Dimethyl (2S,5S,6R)-2-(acetoxymethyl)-5,6-dihydro-2H-pyran-5,6-bisacetate (**35**). — Prepared in benzene for 4 d at 60° (yield 13%), $[\alpha]_D^{25}$ −106.5° (*c* 0.555, chloroform); $\nu_{max}^{CHCl_3}$ 3000, 1760, 1430, 1370, 1200, and 980 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.77 (br. d, 1 H, *J* 10.4 Hz, H-4 or -5), 5.67 (br. d, 1 H, *J* 10.4 Hz, H-4 or -5), 4.33 (m, 1 H, H-6), 4.07 (m, 1 H, CH_2OAc), 3.77 (td, 1 H, *J* 8.5, 3.7 Hz, H-2), 3.69 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 2.63 (m, 2 H, CH_2CO_2, H-3), 2.53 (dd, 1 H, *J* 16.3, 9.1 Hz, CH_2CO_2), 2.37 (dd, 1 H, *J* 15.9, 4.8 Hz, CH_2CO_2), 2.18 (dd, 1 H, *J* 15.9, 4.8 Hz, CH_2CO_2), and 2.05 (s, 3 H, $OCOCH_3$); m.s.: *m/z* 269, 240, 227, 167, and 153; m.s. calc. for $C_{13}H_{17}O_6$ (M − OCH_3), 269.1205; found, 269.1204.

Anal. Calc. for $C_{14}H_{20}O_7$: C, 56.00; H, 6.71; Found: C, 55.91; H, 6.86.

Methyl cis*-4-acetoxy-2-cyclohexene-1-acetate*. — Prepared in benzene for 18 h at 60° and purified by chromatography in 1:3 ethyl acetate–hexane. This monoester was isolated from a mixture of **38** and **39** by the methylation procedure described for **9** (yield 25%); $\nu_{max}^{CHCl_3}$ 3000, 2940, 1720, 1500, 1430, 1370, 1220, 1000, and 700 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.85 (dd, 1 H, *J* 10, 1 Hz), 5.78 (m, 1 H), 5.22 (m, 1 H), 3.71 (s, 3 H), 2.58 (m, 1 H), 2.41 (dd, 1 H, *J* 15, 6 Hz), 2.34 (dd, 1 H, *J* 15, 7 Hz), 2.34 (dd, 1 H, *J* 15, 7 Hz), 2.06 (s, 3 H), and 1.9–1.7 (m, 4 H); m.s.: *m/z* 170 (M^+), 153, 152, 139, and 96; m.s. calc. for $C_9H_{14}O_3$, 170.0943; found, 170.0943.

Dimethyl cis*-3-cyclohexene-1,2-diacetate*. — This diester was isolated from a mixture of **38** and **39** by the methylation procedure described for **9** (yield 10%): $\nu_{max}^{CHCl_3}$ 2925. 1730, 1435, 1300–1160, 1000, and 700 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$):δ 5.17 (m, 1 H), 5.56 (m, 1 H), 4.69 (s, 3 H), 4.68 (s, 3 H), 2.77 (m, 1 H), 2.4–2.14 (m, 6 H), 2.06 (m, 1 H), and 1.70–1.4 (m, 2 H); m.s.: *m/z* 226 (M^+), 195, 194, and 152; m.s. calc. for $C_{12}H_{18}O_4$, 226.1205; found, 226.1205.

Methyl 5,6-dihydro-2H-pyran-2-acetate. — Prepared in chloroform for 30 min at 60° (yield 60.3%), $\nu_{max}^{CHCl_3}$ 3000–2850, 1730, 1430, 1360, 1280–1160, 1080, 990, and 700 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.9 (m, 1 H), 5.66 (ddd, 1 H, *J* 10, 5, 2.5 Hz), 4.56 (m, 1 H), 3.96 (m, 1 H), 3.70 (s, 3 H), 3.71–3.65 (m, 1 H), 2.59 (dd, 1 H, *J* 15.8, 7.5 Hz), 2.48 (dd, 1 H, *J* 15, 5 Hz), 2.35–2.16 (m, 1 H), and 1.96 (d, 1 H, *J* 15 Hz); m.s.: *m/z* 156 (M^+), 124, 96, 83, 82, 58 and 43; m.s. calc. for $C_8H_{12}O_3$, 156.0786; found, 156.0784.

Anal. Calc. for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.29; H, 7.72.

Methyl (2R,5S)-5-[bis(ethoxycarbonyl)methyl]-5,6-dihydro-2H-pyran-2-acetate (**48**). — Prepared from **9** (68 mg) by the procedure described for **56** and purified by l.c. (1:4 ethyl acetate–hexane) to give 133 mg (96%), clear oil, $[\alpha]_D^{25}$ −115° (*c* 0.480, chloroform); $\nu_{max}^{CHCl_3}$ 3000, 1730, 1440, 1380, 1300, 1180, 1100, and 1040 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.86 (ddt, 1 H, *J* 10, 5, 1.5 Hz, H-4), 5.78 (dt, 1 H, *J* 10, 1 Hz, H-3), 4.53 (m, 1 H, H-2), 4.2 (m, 4 H, CO_2CH_2), 3.89 (dt, 1 H, *J* 12, 1.5 Hz, H-6*e*), 3.77 (dd, 1 H, *J* 12, 4 Hz, H-6*a*), 3.72 (s, 3 H, OCH_3), 3.55 [d, 1 H, *J* 10 Hz, $CH(CO_2Et)_2$], 2.78 (m, 1 H, H-5), 2.56 (dd, 1 H, *J* 15, 8 Hz, CH_2CO_2), 2.48 (dd,

1 H, *J* 15, 5 Hz, CH_2CO_2), and 1.3 (overlapping t, 6 H, 2 $CO_2CH_2CH_3$); m.s.: *m/z* 283, 251, and 154; m.s. calc. for $C_{13}H_{17}O_6$ (M − OEt), 269.1025; found, 269.1025.

Anal. Calc. for $C_{15}H_{22}O_7$: C, 57.35; H, 7.06. Found: C, 57.15; H, 7.01.

Methyl (2S,3R,4R,5S)-5-[bis(ethoxycarbonyl)methyl]-3,4-dihydroxytetrahydropyran-2-acetate (**49**). — This compound was prepared, by the procedure described for **57**, from **48** (60 mg, 0.19 mmol) to give 65.5 mg (99%), clear oil, $[\alpha]_D^{25}$ −15.8° (*c* 0.576, chloroform); $\nu_{max}^{CHCl_3}$ 3550, 3000, 1740, 1480, 1450, 1380, 1310, 1250, 1190, 1110, 1070, 1030, and 860 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 4.2 (m, 2 H), 4.0–3.85 (m, 2 H), 3.71 (s, 3 H), 3.60 (m, 2 H), 3.02 (m, 2 H), 2.81 (dd, 1 H, *J* 16, 4 Hz), 2.62 (d, 1 H, *J* 12 Hz), 2.54 (dd, 1 H, *J* 14, 8 Hz), and 1.27 (q, 6 H, *J* 8 Hz); m.s.: *m/z* 330, 317, and 161; m.s. calc. for $C_{15}H_{22}O_8$ (M − H_2O), 330.1315; found, 330.1315.

Methyl (2S,3R,4R,5S)-3,4-diacetoxy-5-[bis(ethoxycarbonyl)methyl]tetrahydropyran-2-acetate (**50**). — $[\alpha]_D^{25}$ −14.8° (*c* 0.426, chloroform); $\nu_{max}^{CHCl_3}$ 1735 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.31 (br. t, 1 H, *J* 3 Hz, H-4), 4.86 (dd, 1 H, *J* 10, 7 Hz, H-3), 4.4–4.2 (m, 4 H, CO_2CH_2), 3.98 (dd, 1 H, *J* 12.6, 3 Hz, H-6*e*), 3.77 [d, 1 H, *J* 11.1 Hz, $CH(CO_2Et)_2$], 3.75 (d, 1 H, *J* 12.6 Hz, H-6*a*), 3.72 (s, 3 H, OCH_3), 2.62 (br. d, 1 H, H-5), 2.55 (dd, 1 H, *J* 16, 9 Hz, CH_2CO_2), 2.47 (dd, 1 H, *J* 16, 3.7 Hz, CH_2CO_2), 2.12 (s, 3 H, $OCOCH_3$), 1.98 (s, 3 H, $OCOCH_3$), 1.34 (t, 3 H, $CO_2CH_2CH_3$), and 1.28 (t, 3 H, $CO_2CH_2CH_3$); m.s.: *m/z* 433 (M + H) and 387; m.s. calc. for $C_{18}H_{25}O_{10}$ (M − OCH_3), 401.1448; found, 401.1448.

Anal. Calc. for $C_{19}H_{28}O_{11}$: C, 52.78; H, 6.52. Found: C, 52.61; H, 6.33.

Methyl (2S,3R,4R,5S)-3,4-dibenzoyloxy-5-[bis(ethoxycarbonyl)methyl]tetrahydropyran-2-acetate (**51**). — $\nu_{max}^{CHCl_3}$ 1735 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 8.03 (dd, 2 H, *J* 8, 2 Hz), 7.85 (dd, 2 H), 7.6–7.2 (m, 6 H), 5.68 (br. t, 1 H, *J* 3.0 Hz), 5.22 (dd, 1 H, *J* 9.8, 3.1 Hz), 4.47 (ddd, 1 H, *J* 9.8, 8.1, 5.0 Hz), 4.35 (m, 2 H), 4.22 (m, 2 H), 4.19 (dd, 1 H, *J* 12, 3 Hz), 3.93 (d, 1 H, *J* 10.9 Hz), 3.88 (dt, 1 H, *J* 12, 1 Hz), 3.65 (s, 3 H), 2.87 (br. d, 1 H, *J* 10.9 Hz), 2.64 (dd, 1 H, *J* 15.3, 5 Hz), 2.61 (dd, *J* 15.3, 8.1 Hz), 2.37 (t, 3 H), and 1.29 (t, 3 H); m.s.: *m/z* 511, 319, and 274; m.s. calc. for $C_{28}H_{29}O_{10}$ (M − OCH_3), 525.1759; found, 525.1761.

Methyl (2R,4R)-5-[bis(ethoxycarbonyl)methyl]-5,6-dihydro-2H-pyran-2-acetate (**53**). — By the procedure described for **56, 33** (9.4 mg) gave a 9:5 mixture of **53** and regioisomer **54** (5.7 mg, 42%). Flash-column chromatography of the mixture on silica gel with 1:2 ethyl acetate–hexane gave pure **53** (3.9 mg, 29%), clear oil; $\nu_{max}^{CHCl_3}$ 2980, 1720, 1440, 1370, 1330, 1300–1160, 1020, and 850 cm^{-1}; ^{1}H-n.m.r. (C_6D_6): δ 5.90 (dt, 1 H, *J* 12, 2.5 Hz, H-3 or -4), 5.50 (dt, 1 H, *J* 12, 2 Hz, H-3 or -4), 4.56 (m, 1 H, H-2), 4.0–3.8 (m, 5 H, CO_2CH_2, H-6), 3.57 (dd, 1 H, *J* 12, 7 Hz, H-6), 3.32 [d, 1 H, *J* 7.5 Hz, $CH(CO_2Et)_2$], 3.30 (s, 3 H, OCH_3), 3.14 (m, 1 H, H-5), 2.49 (dd, 1 H, *J* 18, 12 Hz, CH_2CO_2), 2.14 (dd, 1 H, *J* 18, 6 Hz, CH_2CO_2), and 0.94–0.97 (m, 6 H, 2 $CO_2CH_2CH_3$).

Isomer **54** could not be isolated in pure form. The following peaks were assigned from the ^{1}H-n.m.r. spectrum (C_6D_6) of the mixture: δ 5.85 (m, 1 H, H-4 or -5), 5.40 (dq, 1 H, *J* 10, 1 Hz, H-4 or -5), 4.4 (m, 1 H, H-2), 3.91 (m, 6 H, CO_2CH_2,

H-6*a*,6*e*), 3.69 [d, 1 H, *J* 7 Hz, $CH(CO_2Et)_2$], 3.33 (s, 3 H, OCH_3), 2.92 (m, 1 H, H-4), 2.60 (dd, 1 H, *J* 15, 10 Hz, CH_2CO_2), 2.39 (dd, 1 H, *J* 15, 5 Hz, CH_2CO_2), and 1.85 (m, 6 H, 2 $CO_2CH_2CH_3$).

*Methyl (2*R,*5*S,*6*S*)-5-[bis(ethoxycarbonyl)methyl]-6-methyl-5,6-dihydro-2*H-*pyran-2-acetate* (**52**). — Prepared by the procedure described for **56**; $\nu_{max}^{CHCl_3}$ 2980, 1725, 1440, and 1370 cm^{-1}; ^{1}H-n.m.r. (C_6D_6): δ 5.84 (dd, 1 H, *J* 10, 5 Hz, H-3), 5.55 (d, 1 H, *J* 10 Hz, H-4), 4.55 (m, 1 H, H-2), 4.15 (br. q, 1 H, H-6), 4.0–3.8 (m, 4 H, 2 CO_2CH_2), 3.69 [d, 1 H, *J* 8 Hz, $CH(CO_2Et)_2$], 3.31 (s, 3 H, OCH_3), 2.74 (m, 1 H, H-5), 2.49 (dd, 1 H, *J* 15, 8 Hz, CH_2CO_2), 2.25 (dd, 1 H, *J* 15, 8 Hz, CH_2CO_2), 1.17 (d, 3 H, *J* 7 Hz, CH_3), 0.91 (t, 3 H, $CO_2CH_2CH_3$), and 0.86 (t, 3 H, $CO_2CH_2CH_3$); m.s.: *m/z* 328 (M^+), 282, 255, and 168.

*(2*R-cis*)-1-(5-Acetoxy-5,6-dihydro-2*H-*pyran-2-yl)-2-propanone*. (**55**). — To a stirred solution of **10** (50.7 mg, 0.25 mmol) in oxolane (1 mL) containing triethylamine (35 μL, 0.25 mmol) at −10° was added a solution of *o*-anisoyl chloride (35 μL, 0.25 mmol) in oxolane (1 mL). The resulting mixture was stirred for 0.5 h at the same temperature and then cooled to −78°. To this was added dropwise methylmagnesium bromide (88 μL, 0.26 mmol, 2.8M in ether). After stirring for 0.5 h, the reaction was quenched with 10% NH_4Cl solution and extracted with ether (2 × 50 mL). The combined extracts were washed with sat. $NaHCO_3$ solution, water, and NaCl solution, and dried ($MgSO_4$). Concentration of the ether solution gave **55** (31.2 mg) clear oil unstable to storage. Flash-column chromatography of the residue with 1:2 ethyl acetate–hexane afforded pure **55** (12.9 mg, 41.2%), colorless oil, $[\alpha]_D^{25}$ −158° (*c* 1.21, chloroform); $\nu_{max}^{CHCl_3}$ 3000, 1715, 1400, 1380, 1200, 1090, and 700 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.97 (m, 2 H, H-3,-4), 5.11 (m, 1 H, H-5), 4.50 (m, 1 H, H-2), 4.06 (d, 1 H, *J* 12.3 Hz, H-6), 3.77 (dd, 1 H, *J* 12.3, 2.8 Hz, H-6), 2.82 (dd, 1 H, *J* 16.6, 7.6 Hz, CH_2CO), 2.59 (dd, 1 H, *J* 16.6, 5.5 Hz, CH_2CO), 2.21 (s, 3 H, $COCH_3$), and 2.09 (s, 3 H, $OCOCH_3$); m.s.: *m/z* 168 (M − HCHO), 138, 126, 96, 81, and 43; m.s.: calc. for $C_9H_{12}O_3$, 168.0786; found, 168.0782.

*Ethyl {3*S-[*3*α-(S*),*6*α]}-6-(2-oxopropyl)-α-(phenylsulfonyl)-3,6-dihydro-2*H-*pyran-2-acetate*[38,40] (**56**). — To oil-free NaH (108 mg, 4.5 mmol) in oxolane (5 mL) was added ethyl phenylsulfonylacetate (1.03 g, 4.4 mmol) in oxolane (5 mL), and the mixture was stirred for 30 min at 25°. To the resulting turbid solution, *N,N*-dimethylformamide (3 mL) was added and the mixture centrifuged under N_2. The clear solution (12.6 mL, 4.36 mmol) was added to a mixture of **55** (439 mg, 2.22 mmol) and $Pd(dppe)_2$ (308 mg) in oxolane (5 mL). The mixture was stirred for 4.5 h and poured into a mixture of ether (50 mL) and dilute $NaHSO_4$ solution (30 mL), and extracted with ether (2 × 100 mL). The combined ether solution was washed with water and NaCl solution, and dried ($MgSO_4$). Flash chromatography of the residue from the concentrated ether solution with 1:1 ethyl acetate–hexane gave a 1:1 mixture (690 mg, 85%) of two isomers as a clear, thick oil; $\nu_{max}^{CHCl_3}$ 3000, 1730, 1600, 1320, 1140, 1080, and 700 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 8.0–7.89 (m), 7.71–7.66 (m), 7.62–7.55 (m), 5.83–5.76 (m), 4.56 (m), 4.21 (d, *J* 5 Hz), 4.20 (d, *J* 5 Hz),

4.0–3.89 (m), 3.76 (dd, *J* 11.9, 3.2 Hz), 3.71 (m), 2.70 (dd, *J* 16.4, 7.9 Hz), 2.69 (dd, *J* 16.4, 7.9 Hz), 2.50 (ddd, *J* 16.4, 5.0, 2.5 Hz), 2.18 (s), 2.17 (s), 1.40 (t, *J* 5 Hz), and 1.20 (t, *J* 5 Hz).

*Ethyl (3*S-cis*)-6-(2-oxopropyl)-3,6-dihydro-2*H*-pyran-2-acetate*[42] (**37**). — To a solution of **56** (197.3 mg, 0.54 mmol) and $NaH_2PO_4 \cdot H_2O$ (298 mg, 2.16 mmol) in methanol (6 mL), cooled to −20°, was added pulverized 6% Na–Hg (0.8 g). The resulting solution was stirred for 30 min at the same temperature and poured into water (10 mL). The aqueous solution was extracted with ether (2 × 100 mL), and the combined ether solution was washed with water and NaCl solution, and dried ($MgSO_4$). Flash-column chromatography of the residue with 1:1 ethyl acetate–hexane afforded pure **57** (99.5 mg, 81%), clear oil, $[\alpha]_D^{25}$ −73° (*c* 1.02, chloroform); $\nu_{max}^{CHCl_3}$ 3000, 1730, 1360, 1250, 1150, 1080, 1010, and 750 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.86 (d, 1 H, *J* 10.1 Hz, H-4), 5.61 (d, 1 H, *J* 10.1 Hz, H-3), 4.54 (m, 1 H, H-2), 4.13 (q, 2 H, *J* 7.1 Hz, CO_2CH_2), 3.75 (m, 2 H, H-6*a*,6*e*), 2.71 (dd, 1 H, *J* 16.0, 8.1 Hz, CH_2CO_2), 2.55–2.39 (m, 4 H, 2 CH_2CO_2), 2.20 (s, 3 H, $COCH_3$), and 1.26 (t, 3 H, *J* 7.3 Hz, $CO_2CH_2CH_3$); m.s.: *m/z* 226 (M^+), 211, 138, and 81; m.s. calc. for $C_{12}H_{18}O_4$, 226.1205; found, 226.1195.

Anal. Calc. for $C_{12}H_{18}O_4$: C, 63.69; H, 8.02. Found: C, 63.56; H, 8.19.

(E)*-4,8-Anhydro-5,6-*O*-cyclohexylidene-1,3,7-trideoxy-7-*C*-(ethoxycarbonyl)methyl-*D-allo*-2-octulose* (**58**). — A mixture of **57** (164 mg, 0.73 mmol), *N*-methylmorpholine-*N*-oxide dihydrate (105.8 mg, 0.77 mmol), water (2 mL), acetone (800 μL), 1,1-dimethylpropanol (300 μL), and a catalytic amount of OsO_4 was stirred for 36 h at 25°. The resulting black mixture was stirred with $NaHSO_4$ (100 mg) for 1 h and diluted with ethyl acetate. The ethyl acetate solution was filtered through Florisil, washed with $Na_2S_2O_3$ solution and NaCl solution, and dried ($MgSO_4$). Concentration of the ethyl acetate solution gave 4,8-anhydro-1,3,7-trideoxy-7-*C*-(ethoxycarbonyl)methyl-D-*allo*-2-octulose[39] (139.1 mg, 73.2%) as a clear oil. Extraction of the aqueous layer (saturated with salt) with ethyl acetate gave additional diol (10.5 mg). This clear oil was used without further purification; $\nu_{max}^{CHCl_3}$ 3700–3150, 2930, 1720, 1360, 1320–1140, 1110, 1060, 940, and 740 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 4.13 (q, 2 H, *J* 7.1 Hz), 4.0–3.85 (m, 3 H), 3.52 (d, 1 H, *J* 11.7 Hz), 3.42 (d, 1 H, *J* 9.3 Hz), 2.82 (dd, 1 H, *J* 16.4, 5.0 Hz), 2.73 (dd, 1 H, *J* 16.4, 7.1 Hz), 2.55 (dd, 1 H, *J* 17.8, 10.1 Hz), 2.41–2.3 (m, 2 H), 2.22 (s, 3 H), and 1.25 (t, 3 H, *J* 7.1 Hz).

A mixture of the diol (134 mg, 0.52 mmol), cyclohexanone (647 μL, 6.24 mmol), anhydrous $CuSO_4$ (497.6 mg, 3.12 mmol), and 4-toluenesulfonic acid (1.5 mg) in benzene (12 mL) was stirred for 30 h at 25°. The mixture was filtered and the solid washed with ether. The residue from concentration of the combined benzene–ether solutions was chromatographed with 1:2 ethyl acetate–hexane to give **58** (146.3 mg, 83%), clear, thick oil, $[\alpha]_D^{25}$ +6.7° (*c* 0.975, chloroform); $\nu_{max}^{CHCl_3}$ 2930, 1720, 1360, 1260–1160, 1110, 1020, 920, and 700 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 4.14 (q, 2 H, *J* 7.1 Hz, CO_2CH_2), 4.07 (s, 1 H), 3.80 (dd, 1 H, *J* 7.1, 2.4 Hz), 3.73 (m, 2 H), 3.61 (d, 1 H, 11.9 Hz), 2.73–2.52 (m, 4 H, CH_2CO_2, CH_2CO),

2.4 (dd, 1 H, *J* 18.6, 9.5 Hz, H-5), 2.18 (s, 3 H, $COCH_3$), 1.8–1.3 (m, 10 H), and 1.25 (t, 3 H, *J* 7.1 Hz, $CO_2CH_2CH_3$); m.s.: *m/z* 340 (M^+), 297, 242, 207, 197, and 185; m.s. calc. for $C_{18}H_{28}O_6$, 340.1886; found, 340.1884.

Anal. Calc. for $C_{18}H_{28}O_6$: C, 63.50; H, 8.29. Found: C, 63.48; H, 8.49.

Ethyl (E)*-5,9-anhydro-6,7-*O*-cyclohexylidene-2,3,4,8-tetradeoxy-8-*C*-(ethoxycarbonyl)methyl-3-methyl-*D-allo*-non-2-enoate* (**59**). — To a stirred solution of excess sodium triethylphosphonoacetate in oxolane (5 mL of a 0.36M solution) at 25° was added a solution of **58** (60 mg, 0.18 mmol) in oxolane (1.5 mL). The mixture was stirred for 15 min at 25°, and then heated for 4 h at 60°. The cooled mixture was poured into ether, washed with NH_4Cl solution and NaCl solution, and dried ($MgSO_4$). Concentration of the ether solution gave a 3:1 mixture of *trans*-(**59**) and *cis*-isomer as a yellow oil. Medium-pressure l.c. on silica gel with 1:9 ethyl acetate–hexane afforded **59** (*E*) 31.8 mg, 43%, clear oil, $[\alpha]_D^{25}$ −8.8° (*c* 0.24, chloroform); $\nu_{max}^{CHCl_3}$ 2940, 1730, 1700, 1640, 1450, 1370, 1340, 1270–1030, 930, and 710 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.73 (d, 1 H, *J* 1 Hz, =C–H), 4.14 (q, 2 H, *J* 6.8 Hz, CO_2CH_2), 4.13 (q, 2 H, *J* 7.1 Hz, CO_2CH_2), 3.77–3.61 (m, 2 H, H-6, -3 or -4), 3.43 (td, 1 H, *J* 9.5, 3.0 Hz, H-3 or -4), 2.61–2.38 (m, 4 H, 2 CH_2CO_2), 2.19 (d, 3 H, *J* 1.2 Hz, CH_3), 2.34–2.16 (m, 1 H, H-5), 1.72–1.26 (m, 10 H), 1.26 (t, 3 H, *J* 7.1 Hz, $CO_2CH_2CH_3$), and 1.26 (t, 3 H, *J* 6.8 Hz, $CO_2CH_2CH_3$); m.s.: *m/z* 410 (M^+), 381, 296, 283, and 267; m.s. calc. for $C_{22}H_{34}O_7$, 340.2305; found, 340.2320.

(E)*-5,9-Anhydro-6,7-*O*-cyclohexylidene-2,3,4-tetradeoxy-8-*C*-(ethoxycarbonyl)methyl-3-methyl-*D-allo*-non-2-enal*[8,13] (**61**). — To a solution of diisobutylaluminumhydride (2.0 mL of a M solution in hexane), cooled to −78°, was added a solution of butyllithium (1.18 mL, 1.7M in hexane). After stirring for 15 min at the same temperature, oxolane (1.6 mL) was added. This mixture (70 μL, 0.03 mmol) was added to a solution of **59** (10.2 mg, 0.03 mmol) in oxolane (0.5 mL), cooled to −78°. The mixture was stirred for 2 h, poured into a mixture of water (3 mL) and dichloromethane (10 mL), and extracted with dichloromethane (10 mL). The combined extracts were washed with NaCl solution, dried ($MgSO_4$), and concentrated to give a clear oil (15.1 mg). Flash-column chromatography of the residue with 1:2 ethyl acetate–hexane afforded **61** (3.5 mg, 38%), **60** (3.5 mg, 38%), and **59** (1.0 mg, 9.8%). Aldehyde[8,13] **61**, $[\alpha]_D^{25}$ −11.3° (*c* 0.32, chloroform); $\nu_{max}^{CHCl_3}$ 2920, 2700, 1720, 1700, 1640, 1440, 1360, 1340, 1210, 1145, 1105, and 1040 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 9.81 (s, 1 H), 5.73 (m, 1 H), 4.15 (q, 1 H, *J* 5 Hz), 4.03 (m, 1 H), 3.80 (dd, 1 H, *J* 11, 3 Hz), 3.68 (dd, 1 H, *J* 9.0, 5.0 Hz), 3.58 (d, 1 H, *J* 12 Hz), 3.45 (td, 1 H, *J* 10, 3 Hz), 2.78 (ddd, 1 H, *J* 15, 6.1 Hz), 2.68 (m, 1 H), 2.60–2.47 (m, 2 H), 2.24–2.17 (m, 1 H), 2.20 (d, 3 H, *J* 1 Hz), 1.75–1.35 (m, 10 H), and 1.30 (t, 3 H, *J* 5 Hz).

(E)*-5,9-Anhydro-6,7-*O*-cyclohexylidene-2,3,4,8-tetradeoxy-8-*C*-(ethoxycarbonyl)methyl-3-methyl-*D-allo*-non-2-enitol*[8] (**60**). — $[\alpha]_D^{25}$ −9.7° (*c* 0.415, chloroform); $\nu_{max}^{CHCl_3}$ 3450, 2910, 1690, 1640, 1430, 1360, 1200, 1140, 1100, and 920 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.73 (m, 1 H), 4.14 (q, 2 H, *J* 7 Hz), 4.08 (m, 1 H), 3.76–3.70 (m, 4 H), 3.60 (dd, 1 H, *J* 11.3 Hz), 3.53 (td, 1 H, *J* 8.3 Hz), 2.51 (d, 1

H, *J* 14 Hz), 2.27–2.0 (m, 2 H), 2.20 (d, 3 H, *J* 1 Hz), 1.82–1.33 (m, 13 H), and 1.27 (t, 3 H, *J* 7 Hz).

*7-O-Acetyl-4,8-anhydro-5,6-O-cyclohexylidene-1,3-dideoxy-*L-talo-*2-octulose* (**62**). — By the procedure described for **58, 55** (132.5 mg, 0.67 mmol) gave 7-*O*-acetyl-4,8-anhydro-1,3-dideoxy-L-*talo*-2-octulose (111.5 mg 72%), clear oil, $\nu_{max}^{CHCl_3}$ 3700–3150, 3000, 1720, 1370, 1200, 1120, and 1040 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 4.88–4.87 (m, 1 H), 4.01 (m, 1 H), 3.90 (d, 1 H, *J* 12.9 Hz), 3.74 (d, 1 H, *J* 12.9 Hz), 3.56 (d, 1 H, *J* 9.3 Hz), 3.10 (s, 1 H), 2.88 (dd, 1 H, *J* 16.4, 4.7 Hz), 2.74 (dd, 1 H, *J* 16.4, 7.1 Hz), 2.23 (s, 3 H), and 2.10 (s, 3 H).

By the procedure described for **58** and flash-column chromatography (1:1 ethyl acetate–hexane), the just described diol (192 mg, 0.83 mmol) gave pure **62** (222 mg, 80%), white crystals; m.p. 79–80°, $[\alpha]_D^{25}$ +1.3° (*c* 1.145, chloroform); $\nu_{max}^{CHCl_3}$ 2940, 1730, 1370, 1240–1200, 1100, 1050, and 930 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.13 (m, 1 H, H-5), 4.14 (m, 1 H, H-4), 3.88–3.84 (m, 2 H), 3.76 (dd, 1 H, *J* 13.3, 1.8 Hz), 3.69 (td, 1 H, *J* 9.3, 3.4 Hz), 2.73 (dd, 1 H, *J* 16, 3.4 Hz, CH_2CO), 2.63 (dd, 1 H, *J* 16.8, 8.9 Hz, CH_2CO), 2.20 (s, 3 H, $COCH_3$), 2.11 (s, 3 H, $OCOCH_3$), and 1.74–1.25 (m, 10 H); m.s.: *m/z* 312 (M^+), 269, 252, 214, 171, and 155; m.s. calc. for $C_{16}H_{24}O_6$, 312.1573; found, 312.1582.

Anal. Calc. for $C_{16}H_{24}O_6$: C, 61.65; H, 7.74. Found: C, 61.63; H, 7.67.

*4,8-Anhydro-5,6-O-cyclohexylidene-1,3-dideoxy-2-C-(ethoxycarbonyl)methyl-*L-talo-*7-octulose* (**63**). — This compound was obtained by the procedure described for **59**, and flash-column chromatography (1:1 ethyl acetate–hexane) of **32** (10.1 mg, 0.03 mmol) gave a 4:1 mixture of *trans* and *cis* isomers (8.5 mg, 90%), clear oil, $[\alpha]_D^{25}$ −9.3° (*c* 1.24, chloroform); $\nu_{max}^{CHCl_3}$ 2940, 2850, 1740, 1700, 1640, 1440, 1370, 1240–1200, 1150, 1100, 1040, and 700 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$):δ 5.75 (d, *J* 0.8 Hz), 5.11 (m), 4.17–4.10 (m), 3.87–3.81 (m), 3.65 (dd, *J* 13.3, 2.1 Hz), 3.36 (td, *J* 9.8, 2.3 Hz), 2.55 (d, *J* 14.5 Hz), 2.30–2.19 (m), 2.19 (d, *J* 1.2 Hz), 2.11 (s), 1.95 (d, *J* 1.4 Hz), 1.71–1.31 (m), and 1.29–1.23 (t, *J* 7.1 Hz); m.s.: *m/z* 382 (M^+), 353, 339, 255, and 208; m.s. calc. for $C_{20}H_{30}O_7$, 382.1992; found, 382.1991.

Anal. Calc. for $C_{20}H_{30}O_7$: C, 62.91; H, 7.90. Found: C, 62.82; H, 7.98.

To a stirred solution of sodium ethoxide (catalytic amount) in absolute ethanol (0.8 mL) was added a solution of the just described acetate (25.8 mg, 0.07 mmol) in absolute ethanol (0.8 mL) at 0°. The mixture was stirred for 2 h at the same temperature and poured into sat. NH_4Cl solution, and extracted with ethyl acetate. The extract was washed with NaCl solution, dried ($MgSO_4$), and evaporated to give the alcohol (23.4 mg 100%), clear oil, $\nu_{max}^{CHCl_3}$ 3550, 2930, 1700, 1640, 1440, 1360, 1200, 1140, 1100, 1040, and 930 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.76 (s), 5.74 (s), 4.24–4.22 (m), 4.14 (q, *J* 7.1 Hz), 4.12 (q, *J* 7.12 Hz), 4.0–3.67 (m), 3.50–3.46 (m), 3.38 (td, *J* 9.5, 2.9 Hz), 2.98–2.96 (m), 2.54 (d, *J* 14.4 Hz), 2.27–2.11 (m), 2.19 (d, *J* 1.0 Hz), 1.94 (d, *J* 1.4 Hz), 1.71–1.32 (m), 1.27 (t, *J* 7.1 Hz), and 1.25 (t, *J* 7.1 Hz); m.s.: *m/z* 340 (M^+), 311, 295, 251, 224, and 213; m.s. calc. for $C_{18}H_{28}O_6$, 340.1886; found, 340.1878.

To a stirred solution of the just described alcohol (65.3 mg, 0.19 mmol) and

triethylamine (80 μL, 0.57 mmol) in 1:1 dichloromethane–dimethyl sulfoxide (1.3 mL), cooled to 0°, was added SO_3–pyridine complex (91.6 mg, 0.57 mmol) in 1:1 dichloromethane–dimethyl sulfoxide[48] (800 μL). The resulting solution was stirred for 5 h at the same temperature, poured into sat. NH_4Cl solution (10 mL), and extracted with ethyl acetate (60 mL). The combined ethyl acetate solution was washed with sat. NH_4Cl solution, water, and NaCl solution, dried ($MgSO_4$), and concentrated to give a clear oil (58.3 mg). Flash-column chromatography of the residue with 1:2 ethyl acetate–hexane afforded a 4:1 mixture of *trans* and *cis* isomers of **63** (31.7 mg, 63.6% based on recovered starting material), which were separable by chromatotron (1:4 ethyl acetate–hexane).

E-*isomer*. $[\alpha]_D^{25}$ +11.0° (*c* 0.345, chloroform); $\nu_{max}^{CHCl_3}$ 2925, 2858, 1740, 1640, 1440, 1360, 1200, 1150, 1100, 1040, and 920 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.77 (s, 1 H, =C–H), 4.60 (d, 1 H, *J* 7.9 Hz, H-4), 4.39 (t, 1 H, *J* 8.1 Hz, H-3), 4.31 (d, 1 H, *J* 18 Hz, H-6), 4.17 (q, 2 H, *J* 7.1 Hz, CO_2CH_2), 4.04 (dd, 1 H, *J* 18, 1.4 Hz, H-6), 3.49 (td, 1 H, *J* 8.9, 3.8 Hz, H-2), 2.63 (dd, 1 H, *J* 14.1, 4.2 Hz, CH_2CO_2), 2.47 (dd, 1 H, *J* 14.7, 8.9 Hz, CH_2C=), 2.22 (d, 3 H, *J* 1.2 Hz, CH_3), 2.22–1.30 (m, 10 H), and 1.28 (t, 3 H, *J* 7.0 Hz, $CO_2CH_2CH_3$); m.s.: *m/z* 338 (M^+), 309, 295, 240, and 211; m.s. calc. for $C_{18}H_{26}O_6$, 338.1729; found, 338.1731.

Z-*isomer*. ^{1}H-n.m.r. ($CDCl_3$): δ 5.81 (s, 1 H), 4.62 (d, 1 H, *J* 7.8 Hz), 4.51 (t, 1 H, *J* 7.9 Hz), 4.31 (d, 1 H, *J* 18 Hz), 4.15 (q, 2 H, *J* 7.1 Hz), 4.02 (dd, 1 H, *J* 7.8, 1.2 Hz), 3.65–3.58 (m, 1 H), 3.18–3.15 (m, 1 H), 1.96 (d, 3 H, *J* 1.4 Hz), 2.0–1.32 (m, 10 H), and 1.27 (t, 3 H, *J* 7.1 Hz).

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SYNTHESIS OF *C*-GLYCOSYL COMPOUNDS FROM 3,4,6-TRI-*O*-ACETYL-1,5-ANHYDRO-D-*arabino*-HEX-1-ENITOL AND ALLYLTRIMETHYLSILANE AND BIS(TRIMETHYLSILYL)ACETYLENE

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ABSTRACT

C-Glycosyl derivatives of compounds bearing two, three, or four carbon atoms were obtained from 3,4,6-tri-*O*-acetyl-1,5-anhydro-D-*arabino*-hex-1-enitol (**1**) *via* a deacetoxylated oxonium ion generated by treatment with a Lewis acid. The nucleophilic reagents with this cation were bis(trimethylsilyl)acetylene, allyltrimethylsilane, and furan, which were found to exhibit a higher reaction velocity than **1** itself, a potential nucleophile leading to polymerization.

INTRODUCTION

Carbohydrate compounds have frequently been used as chiral starting materials for the synthesis of natural products by utilizing the chiral center existing in the original skeleton[1], and for asymmetric induction in the side-chain linked to the cycle. Thus, we have demonstrated the use of carbohydrate starting materials in the syntheses of the Prelog–Djerassi lactonic acid[2], of an ansamacrolactam, maytansine[3], and of a marine polyether, namely, okadaic acid[4]. We describe herein the preparation of the key intermediates (**3, 7,** and **10**) for the synthesis of polyethers by *C*-glycosyl intermediates of 3,4,6-tri-*O*-acetyl-1,5-anhydro-D-*arabino*-hex-1-enitol[5] (**1**).

RESULTS AND DISCUSSION

In our synthetic studies on okadaic acid[5], compound **1** was chosen as the starting material for *C*-glycosyl formation, since its cation (**2**) is readily generated under mild conditions by treatment with Lewis acids, such as boron trifluoride etherate, titanium tetrachloride, etc. Generation of **2** in the presence of a nucleophile would produce adduct(s) if the nucleophile attacks **2** much faster than does the starting vinyl ether **1** (ref. 6). Danishefsky *et al.*[7] reported that **1** when treated

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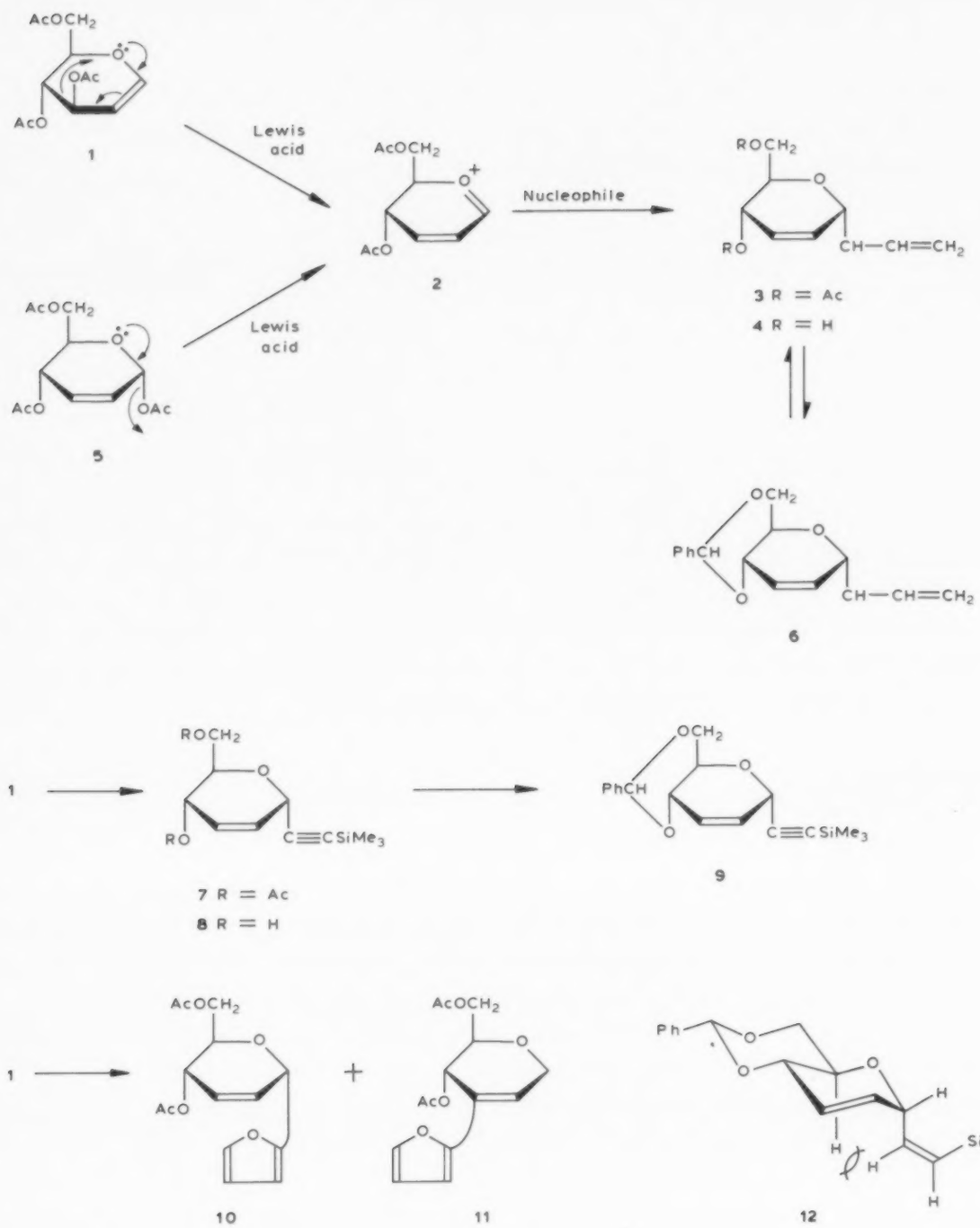

with allyltrimethylsilane [(3-propenyl)trimethylsilane][8] in the presence of titanium tetrachloride gives **3** in 85% yield as a mixture of α- and β-D anomers in a 16:1 ratio. These authors did not report experimental details nor physical data, such as optical rotation. We have reproduced the same experiment[5], but under a nitrogen atmosphere, to obtain a similar result. The ratio of α- to β-D anomer of **3** was 94:6 when the reaction was catalyzed by boron trifluoride etherate. Essentially no condition afforded exclusively the pure α anomer without chromatographic separation, even in the presence of other Lewis acids such as titanium or tin tetrafluoride. This

mixture of anomers was not pure enough as starting material for the synthesis of okadaic acid[5]. An attempt to separate, by l.c. on silica gel, this mixture, only afforded less than one gram of the α and 30 mg of the β anomer. The latter was used for stereochemical studies *(vide infra)*[8]. It was evident that the l.c. technique was inconvenient for the molar-scale purification required for the synthesis of okadaic acid[5]. The pure α anomer **3** was eventually prepared without chromatographic separation, as it was found to be convertible into a crystalline benzylidene derivative **6** by hydrolysis of the mixture of anomers with triethylamine in methanol, and benzylidenation with benzaldehyde dimethyl acetal in the presence of camphorsulfonic acid[9]. Pure **6** was hydrolyzed with acetic acid to give **4**, further acetylated into pure **3**. In this synthesis, participation of the cation **2** was demonstrated by the observation that a similar, unsaturated compound, 1,4,6-tri-*O*-acetyl-α-D-*erythro*-hex-2-enopyranose (**5**), when subjected to the same conditions, afforded **3** in the same ratio of α to β anomer (94:16). The same ratio of products was also observed when the reaction was carried out on a 1:1 mixture of the α and β anomers of **5** (in 80% yield).

Bis(trimethylsilyl)acetylene reacted, as nucleophile, with the cation **2**, which was generated by titanium tetrachloride, to afford an α anomer of **7** in 75% yield. This compound was only obtained when **1** was introduced into the mixture of bis(trimethylsilyl)acetylene and titanium tetrachloride at temperatures <0°. Another Lewis acid, boron trifluoride etherate, afforded only a small proportion of **7** as polymerization of **1** was rapid. Compound **7** was also converted into the crystalline benzylidene derivative **9** by deacetylation with lithium aluminium hydride to give **8**, followed by treatment with benzaldehyde dimethyl acetal[9].

The following nucleophiles were unable to produce *C*-glycosyl compounds owing to rapid polymerization of **1**: trimethylphenylsilane, trimethylvinylsilane, ethynyltrimethylsilane, and dihydropyran. However, furan was found to react with **2** more rapidly than **1**, when treated with boron trifluoride etherate for 2 h at −40°, to give a 1:1 mixture of the 2-(α-D-glycosyl)- (**10**) and 2-(D-glycit-3-yl)-furan (**11**) derivatives, respectively, in 54% yield. The configuration at C-1 of the *C*-glycosyl compounds was found to be mostly in axial orientation, which resulted in the formation of an α-D, axial substituent. The α-D configuration of the propene derivative **3** was proven by comparison of the ^{13}C-n.m.r. spectrum with that of the minor β anomer; the former exhibited chemical shifts at δ 37.8 and 69.7 as compared to the latter at δ 39.4 and 74.2 for C-3 and C-8. These assignments were based on the γ effect in ^{13}C-n.m.r. spectroscopy, which has been often used for distinguishing between epimers[10]. The minor product in the formation of **3** was also shown to have the β configuration by Danishefsky *et al.*[8], by means of a n.O.e. study of the H-1 and H-5 signals in the ^{1}H-n.m.r. spectrum. The configuration of the ethynyl compounds **7–9** was proved also to be α by ^{1}H-n.m.r. spectrometry, as follows. Compound **9** having a fixed configuration was partially reduced into the corresponding dihydro derivative **12**. A clear n.O.e. effect was observed with ~3.5% enhancement between the H signal appearing at δ 6.47 (dd, J 14.2, 9.1 Hz) and the

H-5′ signal at δ 3.70 (ddd, J 10.4, 8.2, 4.4 Hz). This result indicated that the vinyl substituent in **12** is located in α-axial orientation and that the initial reaction with trimethylsilylacetylene had given an α anomer.

Linkage of two, three, or four carbon atom fragments to **1** afforded new possibilities of using this sugar as a chiral starting material for various synthetic targets. The propenyl derivative **3** has been used for the synthesis of okadaic acid[5] and other polyethers[11], and the ethynyl derivative **7** may also be utilized as a precursor of olefins or long carbon-chain molecules.

EXPERIMENTAL

General methods. — Melting points were determined with a Mitamura Giken apparatus and are uncorrected. Optical rotations were measured in 1-dm cells of 2- or 8-mL capacity with a JASCO Model DIP-4 polarimeter. I.r. spectra were recorded with a JASCO A-3 spectrometer. ^{1}H-N.m.r. spectra were recorded at 200 or 500 MHz with JEOL FX200 or GX500 spectrometers for solutions in (^{2}H)chloroform and are reported from the signal of internal tetramethylsilane. 3,4,6-Tri-*O*-acetyl-1,5-anhydro-D-*arabino*-hex-1-enitol (**1**) was prepared from D-glucose[12], and all silicon reagents were purchased from Shin-etsu Chem. Co. Ltd., Niigata, Japan. Elemental analyses were performed by Mr. S. Kitamura of the Analytical Laboratory of this department.

*3-(4,6-Di-*O*-acetyl-2,3-dideoxy-*α*-*D*-*erythro*-hex-2-enopyranosyl)-1-propene* (**3**). — *From* **1**. A solution of **1** (400 g) and allyltrimethylsilane (370 mL) in dichloromethane (4.5 L) was cooled to −50°. It was stirred and BF_3 etherate was added dropwise over 30 min. The stirring was continued for 1 h at −50°, and for 2.5 h at 0°. The mixture was poured into aqueous $NaHCO_3$ with vigorous stirring and the product extracted with dichloromethane. The extracts were dried (Na_2SO_4) and evaporated under reduced pressure to afford **3** and its isomer in quantitative yield (475.2 g, ratio 94:16) as an oil, and this material was used without further purification; ^{13}C-n.m.r. (**3**): δ 20.7, 20.9, 37.8, 62.8, 64.9, 69.7, 71.2, 117.2, 123.7, 132.5, 133.9, 169.8, and 170.1; (minor β-D anomer) 20.7, 20.9, 39.4, 63.6, 65.5, 74.2 (2 C), 117.4, 125.0, 132.0, 133.1, 169.8, and 170.4.

From **6**. Recrystallized **6** (0.25 g) was dissolved in acetic acid (3 mL) and water (1 mL), and heated for 24 h at 55°. The mixture was evaporated to dryness, the residue treated overnight at room temperature with acetic anhydride (1.5 mL) and pyridine (3 mL), and the mixture evaporated *in vacuo* and separated by silica gel t.l.c. to afford pure **3** (85% overall yield); $[\alpha]_D^{20}$ +62.3° (c 1.03, chloroform); $\nu_{max}^{CHCl_3}$ 1740 cm^{-1}; ^{1}H-n.m.r. (200 MHz): δ 2.09 (3 s, H_2), 2.2–2.6 (H_2-3), 3.95 (td, J 6, 4 Hz, H-5′), 4.1–4.25 (H-6′), 4.29 (m, H-1), 5.05–5.2 (H-1,1,4′), and 5.75–6.0 (H-2,2′,3′).

Anal. Calc. for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.40; H, 7.21.

*3-(2,3-Dideoxy-*α*-*D*-*erythro*-hex-2-enopyranosyl)-1-propene* (**4**). — *From* **3**. To a solution of **3** (475.2 g) in methanol (3.2 L) were added triethylamine (650 mL)

and water (550 mL). The solution was stirred at room temperature for two days and the solvent removed under reduced pressure to give crude **4** (22.54 g, yield 89%, in 2 steps from **1**) which was used directly without further purification.

From **6**. Hydrolysis of pure **6** afforded an analytically pure sample of **4**, $[\alpha]_D^{20}$ −35.1° (*c* 0.85, chloroform); ^{1}H-n.m.r. (200 MHz): δ 2.2–2.55 (m, 2 H), 2.8 (br, 1 H, OH), 3.1 (br, 1 H, OH), 3.5 (m, 1 H), 3.7–3.9 (m, 2 H), 4.10 (br. d, 1 H, *J* 8 Hz), 4.23 (br. t, 1 H, *J* 7 Hz), 5.05–5.2 (m, 2 H), and 5.7–5.95 (m, 3 H).

Anal. Calc. for $C_9h_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.49; H, 8.33.

*3-(4,6-*O*-Benzylidene-2,3-dideoxy-α-*D*-*erythro*-hex-2-enopyranosyl)-1-propene* (**6**). — To a solution of **4** (99.6 g, 0.585 mol) and dicamphorsulfonic acid (10 g) in dichloromethane (1.2 L) was added benzaldehyde dimethyl acetal[9] (170 mL, 1.01 mmol) dropwise and the mixture stirred at room temperature overnight. The solvent (120 mL) was removed by heating until t.l.c. analysis showed the absence of the starting material. The mixture was cooled to room temperature and then poured into sat. $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4), and passed through a short column of silica gel. Evaporation under reduced pressure afforded crude crystals (251.1 g) and recrystallization from ether and hexane gave **6** (121 g, yield 80%), white needles, m.p. 63.0°, $[\alpha]_D^{20}$ +26.7° (*c* 1.25, chloroform); ^{1}H-n.m.r. (200 MHz): δ 2.25–2.60 (m, H_2-3), 3.62 (ddd, *J* 10, 8, 4 Hz, H-5′), 3.77 (t, *J* 10 Hz, H-6′), 4.14 (dq, *J* 8, 2 Hz, H-1′), 4.23–4.38 (m, H-4′,6′), 5.09 (br.s, H-1), 5.16 (dq, *J* 8, 1 Hz, H-1), 5.59 (s, PhCH), 5.76 (dt, *J* 10, 2 Hz, H-2′), 5.75–5.94 (m, H-2), 6.01 (br.d, *J* 10 Hz, H-3′), and 7.3–7.6 (5 H, Ar).

Anal. Calc. for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.37; H, 7.03.

*1-(4,6-Di-*O*-acetyl-2,3-dideoxy-α-*D*-*erythro*-hex-2-enopyranosyl)-3,3-dimethyl-3-sila-1-butyne* (**7**). — To a solution of bis(trimethyl)acetylene (1.26 g, 7.4 mmol) and $TiCl_4$ (0.4 mL, 3.7 mmol) in dichloromethane (10 mL), cooled to −20° under N_2 atmosphere, was slowly added, overnight with stirring, a solution of **1** (1.0 g, 3.7 mmol) in dichloromethane (30 mL). The mixture was stirred for an additional 2 h at −20° and then poured into 10% potassium sodium tartrate (40 mL), stirred for 3 h, and extracted dichloromethane (3 ×). The combined organic layers, washed with aq. $NaHCO_3$ and sat. NaCl, dried (Na_2SO_4), and evaporated under reduced pressure, gave a crude oil (1.65 g). Purification by silica gel column chromatography afforded **7** (0.85 g, 75% yield) as an oil, which became crystalline in a freezer, m.p. 43°, $[\alpha]_D^{20}$ −82.0° (*c* 1.00, chloroform); ν_{max}^{film} 3000, 2200, 1740, 1730 cm^{-1}; ^{1}H-n.m.r. (200 MHz): δ 0.20 (s, 9 H), 2.10 (s, 6 H), 4.12 (m, 1 H), 4.24 (m, 2 H), 4.96 (m, 1 H), 5.3 (ddd, 1 H, *J* 10, 4, 2 Hz), 5.77 (dt, 1 H, *J* 10, 2 Hz), and 5.90 (ddd, 1 H, *J* 10, 3, 2 Hz); ^{13}C-n.m.r.: δ 0.24, 21.0, 21.2, 63.2, 64.6, 64.9, 70.2, 91.8, 101.1, 125.7, 129.2, 170.3, and 170.8; m.s.; *m/z* 250 (M^+ − AcOH) and 209 (M^+ − 101).

Anal. Calc. for $C_{15}H_{22}O_5Si$: C, 58.06; H, 7.10. Found: C, 58.04; H, 7.16.

*1-(2,3-Dideoxy-α-*D*-erythro-hex-2-enopyranosyl)-3,3-dimethyl-3-sila-1-butyne* (**8**). — A solution of **7** (300 mg) in tetrahydrofuran (10 mL) was cooled in an ice bath and mixed with M $LiAlH_4$ in tetrahydrofuran (~1.5 mL). After being stirred for 0.5 h at this temperature, the mixture was poured into 10% tartaric acid (10

mL), extracted with dichloromethane, (3 ×), and the extract washed with water half-saturated with NaCl, dried (Na_2SO_4), and evaporated to give crystals (177 mg, 94% yield), m.p. 90°, $[\alpha]_D^{20}$ −191.7° (*c* 1.00, chloroform); ν_{max}^{film} 3600 and 3400 cm^{-1}; ^{1}H-n.m.r. (200 MHz): δ 0.18 (s, 9 H), 2.15 (br., H-3, OH), 3.75 (m, H-5′), 3.88 (m, H-6′), 4.20 (d, H-4′, *J* 9 Hz), 4.92 (m, H-1′), and 5.84 (m, H-2′,3′).

Anal. Calc. for $C_{11}H_{18}O_3Si$: C, 58.41; H, 7.96. Found: C, 58.39; H, 7.97.

*1-(4,6-O-Benzylidene-2,3-dideoxy-α-*D-erythro-*hex-2-enopyranosyl)-3,3-dimethyl-3-sila-1-butyne* (**9**). — A solution of **8** (1.0 g) in *N,N*-dimethylformamide (30 mL) was stirred with benzaldehyde dimethyl acetal (1.0 mL) in the presence of camphorsulfonic acid (0.10 g) for 6 h at 100°. The mixture was poured into a mixture of $NaHCO_3$ (sat., 30 mL) and ice with stirring, and extracted with ether (3 ×). The combined extracts were washed twice with water and sat. NaCl, and dried (Na_2SO_4). Evaporation of the solvent afforded a crude oil which was separated on a silica gel column (~50 g) with 1:2 ether–hexane as eluant to afford pure **9** (1.24 g, 89% yield), which crystallized on storage in a refrigerator; m.p. 68°, $[\alpha]_D^{20}$ −56.3° (*c* 1.00, chloroform); ν_{max}^{film} 2850 cm^{-1}; ^{1}H-n.m.r. (200 MHz): δ 0.20 (s, $SiMe_3$), 3.76 (m, H-5′), 3.90 (m, H-6′b), 4.18 (m, H-4′), 4.40 (dd, *J* 10, 4 Hz, H-6′a), 4.98 (m, H-1′), 5.62 (s, PhCH), 5.76 (dt, *J* 10, 3 Hz, H-2′), and 6.02 (m, H-3′).

Anal. Calc. for $C_{18}H_{22}O_3Si$: C, 68.79; H, 7.01. Found: C, 68.80; H, 7.17.

*2-(4,6-Di-O-acetyl-2,3-dideoxy-α-*D-erythro-*hex-2-enopyranosyl)furan* (**10**). — ^{1}H-N.m.r. (200 MHz): δ 2.06 (s, 3 H), 2.09 (s, 3 H), 3.35 (s, 1 H), 3.55–3.8 (3 H), 5.3–5.4 (2 H), 5.9–6.1 (2 H, AB), 6.3–6.4 (2 H), and 7.45 (dd, 1 H, *J* 2.1 Hz).

*2-(4,6-Di-O-acetyl-1,5-anhydro-2,3-dideoxy-2-*D-ribo-*hex-1-enit-3-yl) furan* (**11**). — ^{1}H-N.m.r. (200 MHz): δ 1.98 (s, 3 H), 2.09 (s, 3 H), 4.02 (td, *J* 6, 2 Hz, H-3′), 4.14 (dt, *J* 10, 4 Hz, H-5′), 4.25–4.35 (m, H_2-6′), 4.80 (d, *J* 6 Hz, H-2′), 5.05 (dd, *J* 10, 6 Hz, H-4′), 6.13 (dd, *J* 3 Hz, H-3 or 4), 6.33 (dd, *J* 3.2 Hz, H-4 or 3), 6.52 (dd, *J* 6, 2 Hz, H-1), and 7.37 (dd, *J* 2 Hz, H-5).

*1-(4,6-O-Benzylidene-2,3-dideoxy-α-*D-erythro-*hexopyranosyl)-3,3-dimethyl-3-sila-1-butene* (**12**). — Compound **9** (18 mg) and dipotassium azodicarboxylate (100 mg) were dissolved in methanol (4 mL), and to this mixture acetic acid (0.05 mL) was added dropwise under a N_2 atmosphere. The mixture was stirred for 4 h at room temperature and, before workup, additional acetic acid (1 mL) was added. After 30 min, the mixture was poured into sat. $NaHCO_3$ solution and was extracted with dichloromethane (× 3). The combined organic layers were washed (NaCl), dried (Na_2SO_4), and evaporated to dryness, and the residual oil was purified by t.l.c. chromatography to afford **12** and its completely reduced derivative in 1:5 ratio in 50% yield; ^{1}H-n.m.r. (500 MHz): δ 0.17 ($SiMe_3$), 3.70 (ddd, *J* 10.3, 8.1, 4.2 Hz, H-5′), 3.77 (t, *J* 10.3 Hz, H-6′b), 4.15 (ddd, *J* 8.1, 4.0, 2.4 Hz, H-4′), 4.32 (dd, *J* 10.2, 4.2 Hz, H-2′), 4.85 (dddd, *J* 9.1, 2.4, 2.0, 0.9 Hz, H-1′), 5.61 (s, PhCH), 5.64 (dt, *J* 10.3, 2.6 Hz, H-2′), 5.76 (dd, *J* 14.2, 0.9 Hz, H-2), 6.04 (br.d, *J* 10.3 Hz, H-3′), 6.47 (dd, *J* 14.2, 9.1 Hz, H-1), 7.37 (m, 3 H, Ar), and 7.51 (m, 2 H, Ar).

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DIASTEREOSELEKTIVE SYNTHESE VON FUNKTIONALISIERTEN *C*-α- UND -β-GLYKOSYLDERIVATEN DER 2-ACETAMIDO-2-DESOXY-D-GLUCOSE*

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ABSTRACT

2-(2-Acetamido-2-deoxy-α,β-D-glucopyranosyl)ethylamine was prepared from 2-acetamido-2-deoxy-D-glucose in six steps including a Wittig reaction. Reaction of the amine with *p*-nitrophenyldiazonium tetrafluoroborate yielded 3-[2-(2-acetamido-2-deoxy-α,β-D-glucopyranosyl)ethyl]-1-*p*-nitrophenyltriazene, a potential irreversible inhibitor of human β-D-hexosaminidase A.

ZUSAMMENFASSUNG

Ausgehend von 2-Acetamido-2-desoxy-D-glucose wurde über eine Wittig-Olefinierung in einer 6-stufigen Reaktion 2-(2-Acetamido-2-desoxy-α,β-D-glucopyranosyl)ethylamin hergestellt. Durch Umsetzung dieser Verbindung mit *p*-Nitrophenyldiazoniumtetrafluoroborat wurde 3-[2-(2-Acetamido-2-desoxy-α,β-D-glucopyranosyl)ethyl]-1-*p*-nitrophenyltriazen erhalten, ein potentieller irreversibler Inhibitor der menschlichen β-D-Hexosaminidase A.

EINLEITUNG

Funktionell substituierte *C*-Glykosylderivate sind Teilstrukturen zahlreicher Naturstoffe[1,2]. Sie dienen als chirale Ausgangsprodukte und Enzyminhibitoren[3,4]. Während Verfahren zur Synthese von *C*-Glykosylderivaten von Aldohexosen existieren[4–6], wurden bisher nur wenige Methoden zur Herstellung von *C*-Glykosylderivaten von Aminozuckern beschrieben[6,7]. *C*-Glykosylderivate der 2-Acetamido-2-deoxy-D-glucose sollten als Inhibitoren und Affinitätsliganden zur Charakterisierung der aktiven Zentren von Hexosaminidasen sehr nützlich sein.

*Herrn Prof. Saul Roseman zum 65. Geburtstag gewidmet.

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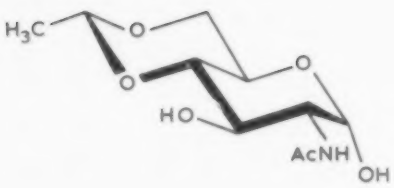
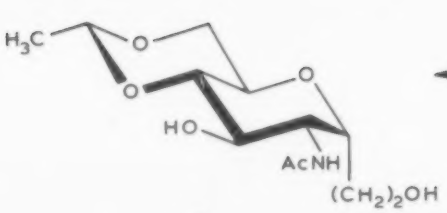


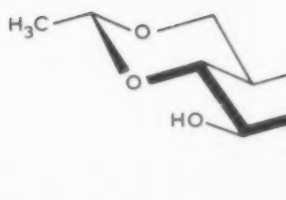
1

$Ph_3P{=}CHCO_2Et$

MeCN



3



4

4 + 5

2

5

6 R = OH ; R', R'' = CH_3CH

7 R = OTs; R', R'' = CH_3CH

8 R = N_3 ; R', R'' = CH_3CH

9 R = NH_2 ; R' = R'' = H

10 R = NH—N=N——NO_2 ; R' = R'' = H

Abb. 1. Oben: ^{13}C-N.m.r. der Verbindung **4** (in $CDCl_3$). Unten: ^{13}C-N.m.r. (Lösung in $CDCl_3$) nach Behandlung der Verbindung **4** mit Natriumethylat in Ethanol.

ERGEBNISSE UND DISKUSSION

Ausgehend vom leicht erhältlichen Derivat 2-Acetamido-2-desoxy-4,6-*O*-ethyliden-α-D-glucose[8] (**1**) wurde ein einfaches Verfahren zur Herstellung von funktionalisierten *C*-Glykosylderivaten der 2-Acetamido-2-desoxy-D-glucose entwickelt. Verbindung **1** liefert mit Ethyl-(triphenylphosphoranyliden)acetat [(Carbethoxymethylen)triphenylphosphoran][9] in siedendem Acetonitril Ethyl-4-acetamido-2,3,4-tridesoxy-6,8-*O*-ethyliden-D-*gluco*-oct-2-enoat (**2**) als *E*/*Z*-Gemisch in ausgezeichneter Ausbeute. Eine *in situ*-Cyclisierung[10] dieser Verbinding wurde unter den Reaktionsbedingungen nicht beobachtet. Behandlung einer verdünnten Lösung von **2** in Ethanol mit Natriumethanolat liefert in einer intramolekularen Michael-Addition Ethyl-(2-acetamido-2-desoxy-4,6-*O*-ethyliden-D-glucopyranosyl)acetat als α/β-Gemisch **4** and **5**. Das α/β-Verhältnis hängt dabei stark von der

Behandlungsdauer mit Natriumethanolat ab: Nach 5–15 Minuten ergibt sich ein α/β-Verhältnis von 9:1 und nach 36 h von 3:10 (s. Abb. 1). Die Verbindung **4** wurde in reiner Form durch fraktionierte Kristallisation aus Diethylether–Ethanol erhalten. Wird sie für 36 h mit Natriumethanolat behandelt, so entsteht ebenfalls das α/β-Gemisch von 3:10.

Die Struktur sowie das α/β-Verhältnis der Anomeren **4** und **5** wurden durch Kombination von ^{1}H-N.m.r.- (400 MHz) und ^{13}C-N.m.r.-Spektroskopie bestimmt. Die endgültige Zuordnung der H-1-Signale im ^{1}H-N.m.r.-Spektrum der Verbindungen **4** and **5** war durch selektive Entkopplungsexperimente möglich. Die thermodynamische Präferenz des β-D-Anomeren spiegelt die Tendenz des C-1-Alkyl-Substituenten wieder, die äquatoriale Position zu besetzen. Die Kopplungskonstante $J_{1,2}$ für H-1 des *C*-Glykosylderivates **5** liegt mit 9 Hz im normalen Bereich. Hingegen wurde für das H-1 des *C*-Glykosylderivates **5** eine auffällig große Kopplungskonstante $J_{1,2}$ 5.6 Hz festgestellt, die in ihrer Größenordnung der für andere *C*-α-D-Glykoside beschriebenen entspricht[6,11].

Bei der basenkatalysierten Umwandlung von **2** bzw. **4** zu **4** und **5** entstehen Nebenprodukte, deren Natur nicht aufgeklärt werden konnte. Das Ausmaß ihrer Bildung hängt von der Dauer der Natriumethanolat-Einwirkung ab. Für die nachfolgend beschriebenen Reaktionen wurde **4/5** mit einem α/β-Verhältnis von 2:1 umgesetzt. Reduktion der Esterfunktion von **4/5** mit $LiBH_4$ führt zum entsprechenden Alkohol **6**. Dabei blieb das α/β-Verhältnis im Produkt **6** gegenüber **4/5** unverändert: Offensichtlich reicht die Basizität des Borhydridanions nicht aus, um eine Anomerisierung zu bewirken. Die Reduktion von reinem **4** mit $LiBH_4$ führt zu **3**, wie das ^{1}H-N.m.r.-Spektrum zeigt (Abb. 2). Auch für dieses *C*-α-D-Glykosylderivat wurde eine große Kopplungskonstante ($J_{1,2}$ 6 Hz) festgestellt. Die selektive Tosylierung der primären Hydroxyfunktion von **6** verlief problemlos. Das *p*-Toluolsulfonat **7** (α,β) bildet sich ohne erkennbare Nebenprodukte und wird mit NaN_3 in *N,N*-Dimethylformamid zum Azid **8** (α,β), umgesetzt. Abspaltung der Ethyliden-Schutzgruppe und Reduktion des Azids zum freien Amin **9** (α,β) wird als Eintopfreaktion durchgeführt.

Analog zur Vorschrift von Sinnot und Smith[12] bildete das Amin **9** (α,β) mit *p*-Nitroanilindiazoniumtetrafluoroborat[13] 3-[2-(2-Acetamido-2-desoxy-α,β-D-glucopyranosyl]ethyl-1-*p*-nitrophenyltriazen (**10**). Wie für andere *C*-Glykosyl-Triazene beschrieben[12,14], ist **10** sehr labil und zerfällt schon bei neutralem pH. Alle Versuche, das Triazen zu isolieren und zu charakterisieren, schlugen fehl. Ein Zerfallsprodukt ist *p*-Nitroanilin, die Identifizierung der anderen ist geplant. Wie erste Versuche zeigen, werden die beiden Zentren[15] der menschlichen β-D-Hexosaminidase A durch das Triazen **10** bereits bei 0° in einer zeitabhängigen Reaktion irreversibel inaktiviert.

EXPERIMENTELLER TEIL

Allgemeine Methoden. — Optische Drehungen: Perkin–Elmer Polarimeter

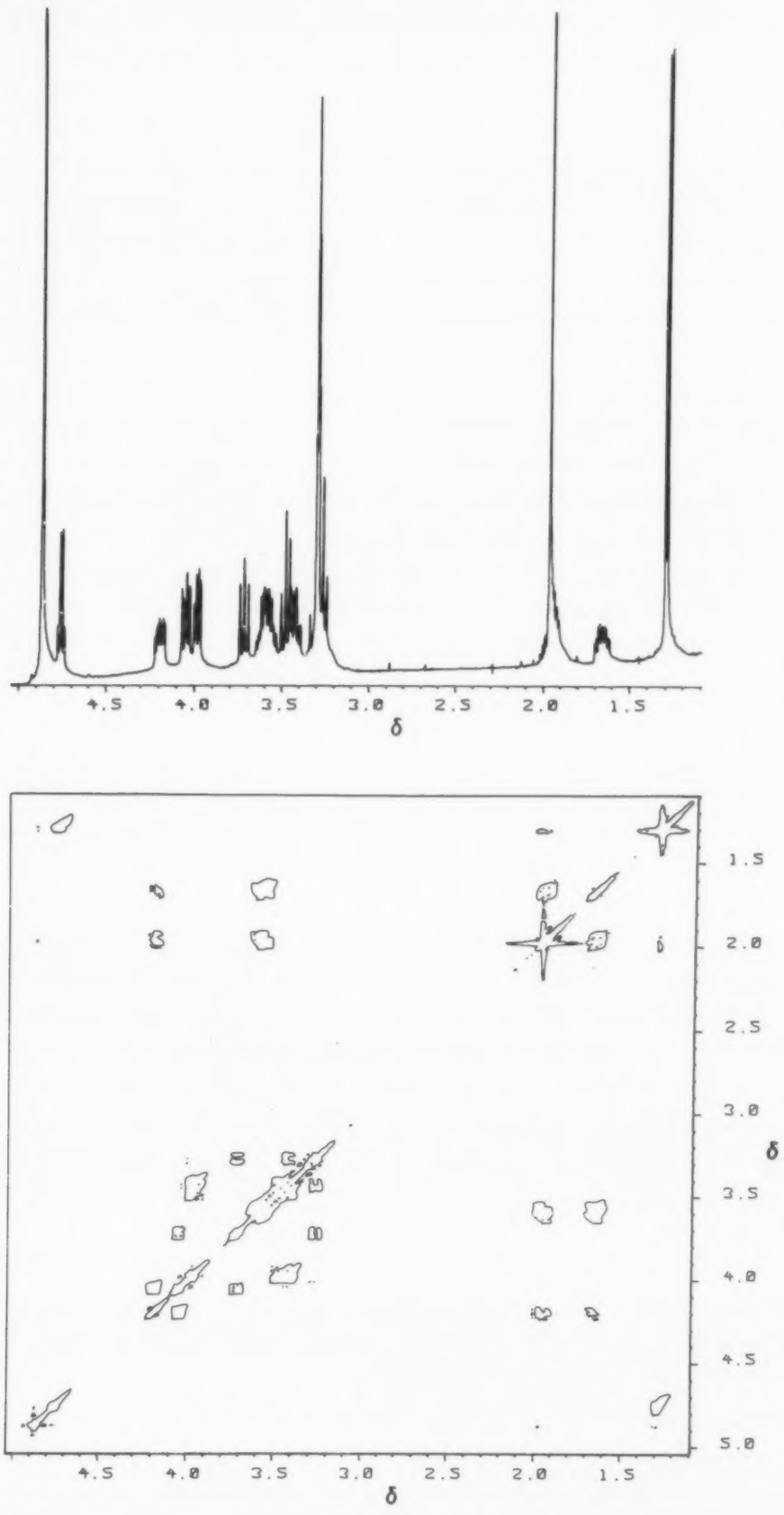


Abb. 2. Zweidimensionale Korrelation der Protonen der Verbindung **6** (α-D-Anomer) in CD_3OD.

241 in 10 cm-Küvetten bei 589 nm. Sämtliche Reaktionen wurden dünnschichtchromatographisch auf Kieselgel-Fertigplatten (Merck) verfolgt. Detektion: Ansprühen mit Essigsäure–H_2SO_4 (9:1, v/v) und anschließende Wärmebehandlung. Säulenchromatographische Trennungen: Lichroprep Si-60 (Korngröße 40–63 μm), Kieselgel 60 (70–230 mesh), Merck. Laufmittel (*A*): Chloroform–Methanol (7:1, v/v); Laufmittel (*B*): Aceton–Tetrachlorkohlenstoff (3:1, v/v). I.r. Spektren: Pye Unicam SP 1025. ^{1}H- und ^{13}C-N.m.r.: Bruker WM 400. Innerer Standard: Tetramethylsilan. Hochaufgelöste Massenspektren: Kratos MS-50.

*2-Acetamido-2-desoxy-4,6-O-ethyliden-α-*D*-glucose*[8] (**1**). — Die Verbindung wurde nach der folgenden modifizierten Vorschrift hergestellt: Fein pulverisierte und über P_2O_5 getrocknete 2-Acetamido-2-desoxy-α,β-D-glucose (11.5 g, 50 mmol) wird in einer Lösung von Acetonitril (140 mL), Paraldehyd (60 mL) und konz. H_2SO_4 (1 mL) suspendiert und das Gemisch für 24 h bei Raumtemperatur gerührt. Anschließend werden eventuell gebildete unlösliche Produkte durch Zusatz von wenig Methanol aufgelöst und die Lösung mit Dowex 1-X8 (OH^-) Anionenaustauscher neutralisiert. Nach Filtrieren und Abdestillieren des Lösungsmittels *in vacuo* entsteht ein kristallines Produkt, aus dem sich **1** (11.5 g, 90%) durch Umkristallisation aus Ethanol–Ethylacetat isolieren läßt. Schmp. 205–207° (Zers.); $[\alpha]_D^{20}$ +59° (*c* 1, Dimethylsulfoxyd); ^{13}C-N.m.r. [($^2H_6$)Me_2SO]: δ 20.32, 22.56, 54.73, 61.95, 67.19, 67.74, 81.95, 91.34, 98.68, 169.44; lit.[7] Schmp. 211–212°, $[\alpha]_D^{25}$ +73° (*c* 1, Dimethylsulfoxyd).

Anal. Ber. für $C_{10}H_{17}NO_6$: C, 48.57; H, 6.92; N, 5.66. Gef.: C, 48.24; H, 6.86; N, 5.58.

*Ethyl-4-acetamido-2,3,4-tridesoxy-6,8-O-ethyliden-*D*-gluco-oct-2-(E,Z)-enoat* (**2**). — 2-Acetamido-2-desoxy-4,6-*O*-ethyliden-α-D-glucose (**1**) (4.94 g, 20 mmol) wird zu einer Lösung von Ethyl-(triphenylphosphoranyliden)acetat [(Carbethoxymethylen)triphenylphosphoran] (7.65 g, 22 mmol) in absol. Acetonitril (100 mL) gegeben und das Reaktionsgemisch für 4 h unter Rückfluß erhitzt. Nach Abdestillieren des Lösungsmittels *in vacuo* kann durch Flash-Chromatographie an Lichroprep Si-60 (Laufmittel *A*) **2** (5.76 g, 92%) als ein 3:1-*E*/*Z*-Gemisch gewonnen werden; R_F 0.5 (Laufmittel *A*); ^{1}H-N.m.r. (400 MHz, $CDCl_3$) (*E*-Isomeres): δ 1.28 (t, 3 H, *J* 7 Hz, CH_3CH_2), 1.31 (d, 3 H, *J* 5 Hz, CH_3CH), 2.07 (s, 3 H, CH_3CONH), 3.30–4.18 (m, 10 H), 4.67 (q, 1 H, *J* 5 Hz, CH_3CH), 6.01 (dd, 1 H, $J_{2,3}$ 15.5, $J_{2,4}$ 2 Hz, H-2), 6.36 (d, 1 H, *J* 9 Hz, NH), 6.93 (dd, 1 H, $J_{2,3}$ 15.5, $J_{3,4}$ 5.8 Hz, H-3); *Z*-Isomeres, charakteristische Signale: δ 1.27 (t, 3 H, *J* 7 Hz, CH_3CH_2), 1.31 (d, 3 H, *J* 5 Hz, CH_3CH), 4.73 (q, 1 H, *J* 5 Hz, CH_3CH), 5.91 (dd, 1 H, $J_{2,3}$ 11.5, $J_{2,4}$ 1.5 Hz, H-2), 6.29 (dd, 1 H, $J_{2,3}$ 11.5, $J_{3,4}$ 8.2 Hz, H-3), 6.61 (d, 1 H, *J* 9 Hz, NH).

Anal. Ber.. für $C_{14}H_{23}NO_7$: C, 52.98; H, 7.30; N, 4.41; *m/z* 318.1553 (M + H)$^+$. Gef.: C, 53.27; H, 7.27; N, 4.18; *m/z* 318.1534.

*Ethyl-(2-acetamido-2-desoxy-4,6-O-ethyliden-α,β-*D*-glucopyranosyl)acetat* (**4** *und* **5**). — Zur Lösung der Verbindung **2** (5 g, 15.77 mmol) in absol. Ethanol (90 mL) wird eine 0.1M ethanolische Natriumethylat-Lösung (10 mL) zugetropft und

das Reaktionsgemisch für 10–15 min kräftig gerührt. Nach Neutralisation mit Dowex 50W-X2 (H^+) Kationenaustauscher, Filtration und Abdestillieren des Lösungsmittels wird **4, 5** (4.9 g, 98%) als α/β-Gemisch im Verhältnis 9:1 gewonnen; R_F 0.57 (Laufmittel *A*). Die reine Verbindung **4** läßt sich durch fraktionierte Kristallisation aus Diethylether–Ethanol isolieren.

Verbindung **4**. $[\alpha]_D^{20}$ +70° (*c* 0.51, Methanol); ^{1}H-N.m.r. (400 MHz, $CDCl_3$): δ 1.26 (t, 3 H, *J* 7.2 Hz, CH_3CH_2O), 1.38 (d, 3 H, *J* 5.2 Hz, CH_3CH), 2.01 (s, 3 H, CH_3CONH), 2.62 (dd, 1 H, $J_{1,7}$ 5.6, $J_{7,7'}$ 14.4 Hz, H-7), 2.70 (dd, 1 H, $J_{1,7'}$ 8.6 Hz, H-7′), 3.30 (s, br., 1 H, OH), 3.32 (dt, 1 H, $J_{3,4}$ 8, $J_{4,5}$ 8 Hz, H-4), 3.45–3.55 (m, 2 H, H-5,6′), 3.77 (dt, 1 H, $J_{2,3}$ 9.6 Hz, H-3), 4.02 (m, 1 H, H-6), 4.10–4.20 (m, 3 H, CH_3CH_2O, H-2), 4.72 (q, 1 H, $J_{1,2}$ 5.6 Hz, H-1), 4.73 (q, 1 H, *J* 5.2 Hz, CH_3CH), 6.21 (d, 1 H, *J* 5 Hz, NH); ^{13}C-N.m.r. ($CDCl_3$): δ 14.21, 20.42, 22.96, 33.09, 54.29, 60.76, 64.55, 68.09, 69.62, 72.23, 81.78, 99.66, 170.90, 171.43.

Verbindung **5**. ^{1}H-N.m.r. [400 MHz, (^{2}H)$CHCl_3$–($^2H_6$)Me_2SO 20:1, v/v]: δ 1.24 (t, 3 H, *J* 7.2 Hz, CH_3CH_2O), 1.36 (d, 3 H, *J* 5.2 Hz, CH_3CH), 1.98 (s, 3 H, CH_3CONH), 2.42 (dd, 1 H, $J_{7,7'}$ 16, $J_{1,7}$ 9 Hz, H-7), 2.49 (dd, 1 H, $J_{1,7'}$ 2.3 Hz, H-7′), 3.23–3.37 (m, 2 H, H-5,6), 3.46 (t, 1 H, $J_{4,5} = J_{3,4}$ 9.6 Hz, H-4), 3.63–3.70 (m, 1 H, H-6′), 3.70–3.85 (m, 2 H, $J_{1,2}$ 9 Hz, H-3,1), 4.04–4.20 (m, 3 H, H-2, CH_3CH_2O), 4.75 (q, 1 H, *J* 5.2 Hz, CH_3CH), 4.79 (d, 1 H, *J* 5.6 Hz, OH), 7.52 (d, 1 H, *J* 7.5 Hz, NH); ^{13}C-N.m.r. ($CDCl_3$): δ 14.16, 20.36, 23.26, 38.07, 55.90, 60.93, 68.16, 70.48, 76.01, 81.31, 99.68, 171.63, 171.95.

Anal. Ber. für $C_{14}H_{23}NO_7$: C, 52.98; H, 7.30; N, 4.41; *m/z* 317.1474 (M^+). Gef.: C, 52.68; H, 7.29; N, 4.49; *m/z* 317.1472.

Basenkatalysierte Anomerisierung der Verbindung **4**. — Eine Lösung von **4** (900 mg) in absol. Ethanol (27 mL) wird mit 0.1M Natriumethylat-Lösung in Ethanol (3 mL) versetzt. Nach 36 h bei Raumtemperatur neutralisiert man mit Dowex 50W-X2 (H^+) Kationenaustauscher. Nach Filtration und Abdestillieren des Lösungsmittels *in vacuo* wird das Produkt folgendermaßen isoliert: (a) Säulenchromatographie an Kieselgel 60 mit Laufmittel *B* und (b) Säulenchromatographie an Kieselgel mit Laufmittel *A*. So wird **4** und **5** (330 mg, 36%) als ein α/β-Gemisch (α:β = 3:10) erhalten, R_F 0.5 (Laufmittel *B*).

*2-(2-Acetamido-2-desoxy-4,6-*O*-ethyliden-α,β-*D*-glucopyranosyl)ethanol* (**6**). — Das Gemisch aus **4** und **5** (**4:5** = 2:1; 3.17 g, 10 mmol) wird in absol. Oxolan (100 mL) gelöst, mit einer M-Lösung von $LiBH_4$ in Oxolan (12 mL) versetzt und für 6 h unter Rückfluß erhitzt. Der Reaktionsverlauf läßt sich dünnschichtchromatographisch verfolgen. Nach Beendigung der Reaktion wird das überschüssige $LiBH_4$ mit 50% Essigsäure zerstört und die Lithiumsalze mit Dowex 50W-X2 (H^+)-Kationenaustauscher entfernt. Anschließend entfernt man die flüchtigen Bestandteile *in vacuo* und isoliert die Verbindung **6** (2.37 g, 75%) als α/β-Gemisch (α:β = 2:1) durch Flash-Chromatographie an Lichroprep Si-60 mit Laufmittel *B*. Alternativ dazu kann das Produkt durch Kristallisation aus Methanol gereinigt werden, R_F 0.32 (Laufmittel *A*); ^{1}H-N.m.r. (400 MHz, CD_3OD): δ 1.30 (d, 3 H, *J* 4.9 Hz, CH_3CH), 1.66 (m, (1 H, H-7), 1.95 (m, 1 H, H-7′), 1.96 (s, 3 H, CH_3CONH), 3.26

(t, 1 H, $J_{3,4} = J_{4,5}$ 9 Hz, H-4), 3.39–3.51 (m, 2 H, H-5,6'), 3.53–3.65 (m, 2 H, CH_2CH_2OH), 3.72 (t, 1 H, $J_{2,3} = J_{3,4}$ 9 Hz, H-6), 3.98 (dd, 1 H, $J_{6,6}$ 10, $J_{5,6}$ 4 Hz, H-6), 4.05 (dd, 1 H, $J_{1,2}$ 6, $J_{2,3}$ 9 Hz, H-2), 4.20 (ddd, 1 H, $J_{1,2}$ 6 Hz, H-1), 4.76 (q, 1 H, *J* 4.9 Hz, CH_3CH); β-D Anomer [charakteristische Signale, $(^2H_6)Me_2SO$]: δ 1.86 (s, 3 H, CH_3CONH), 4.71 (q, 1 H, *J* 4.9 Hz, CH_3CH), 5.08 (d, 1 H, *J* 6 Hz, OH), 7.92 (d, 1 H, *J* 6 Hz, NH).

Anal. Ber. für $C_{12}H_{21}NO_6 \cdot 0.25\ H_2O$: C, 51.51; H, 7.74; N, 5.00; *m/z* 275.1369 (M^+). Gef.: C, 51.50; H, 7.76; N, 4.85; *m/z* 275.1363.

2-(2-Acetamido-2-desoxy-4,6-O-ethyliden-α,β-D-glucopyranosyl)ethyl-1-p-toluolsulfonat (**7**). — Eine Lösung von Verbindung **6** (1.37 g, 5 mmol) in absol. Pyridin (30 mL) wird mit frisch umkristallisiertem *p*-Toluolsulfonsäurechlorid (1.14 g, 6 mmol) bei Raumtemperatur unter Rühren versetzt und das Gemisch für 4 h bei 50° gerührt. Nach Beendigung der Reaktion und Neutralisation mit 5% $NaHCO_3$-Lösung sowie Extraktion mit Dichlormethan (dreimal je 50 mL) werden die organischen Phasen vereinigt, über Na_2SO_4 getrocknet und die flüchtigen Bestandteile *in vacuo* abgezogen. Durch Flash-Chromatographie an Lichroprep Si-60 mit Laufmittel *A* kann **7** (1.95 g, 91%) als ein 2:1-Gemisch gewonnen werden, R_F 0.63 (Laufmittel *A*); ^{1}H-N.m.r. (400 MHz, $CDCl_3$) (α-D Anomer): δ 1.35 (d, 3 H, *J* 5 Hz, CH_3CH), 1.96 (s, 3 H, CH_3CONH), 1.50–2.10 (m, 2 H, CH_2CHOTs), 2.42 (s, 3 H, CH_3–Ph), 3.20–4.80 (m, 11 H), 7.30–7.40 (m, 2 H, arom. H), 7.19 (d, 1 H, *J* 8 Hz, NH), 7.75–7.85 (m, 2 H, arom. H); β-D Anomer (charakteristische Signale): δ 1.32 (d, 3 H, *J* 5 Hz, CH_3CH), 2.02 (s, 3 H, CH_3CONH), 2.44 (s, 3 H, CH_3–Ph), 7.73 (d, 1 H, *J* 8 Hz, NH).

Anal. Ber. für $C_{19}H_{27}O_8S$: *m/z* 429.1458 (M^+). Gef.: *m/z* 429.1460.

2-(2-Acetamido-2-desoxy-4,6-O-ethyliden-α,β-D-glucopyranosyl)-1-azido ethan (**8**). — Verbindung **7** (0.64 g, 1.5 mmol) wird zusammen mit Natriumazid (0.19 g, 3 mmol) in absol. *N,N*-Dimethylformamid (5 mL) für 6 h auf 110° erhitzt. Das Lösungsmittel wird im Hochvakuum abdestilliert und der feste Rückstand mehrmals mit Dichlormethan extrahiert. Durch Flash-Chromatographie an Lichroprep Si-60 mit Laufmittel *A* wird **8** (0.43 g, 97%) als ein α/β-Gemisch (2:1) gewonnen, R_F 0.61 (Laufmittel *A*); ν_{max}^{KBr} 840, 890, 1030, 1095, 1150, 1210, 1295, 1390, 1550, 1645, 2110, 2910, 3420 cm^{-1}; ^{1}H-N.m.r. (400 MHz, CD_3OD) (α-D Anomer): δ 1.31 (d, 3 H, *J* 5 Hz, CH_3CH), 1.97 (s, 3 H, CH_3CONH), 1.60–2.10 (m, 2 H, $CH_2CH_2N_3$), 3.20–4.10 (m, 8 H), 4.16 (ddd, 1 H, $J_{1,2}$ 6 Hz, H-1), 4.74 (q, 1 H, *J* 5 Hz, CH_3CH); (β-D Anomer, charakteristische Signale): δ 1.30 (d, 3 H, CH_3CH), 1.98 (s, 3 H, CH_3CONH).

Anal. Ber. für $C_{12}H_{21}N_4O_5$: *m/z* 301.1512 $(M + H)^+$. Gef.: *m/z* 301.1514.

2-(2-Acetamido-2-desoxy-α,β-D-glucopyranosyl)ethylamin (**9**). — Verbindung **8** (150 mg, 0.5 mol) in 0.2M wäßriger H_2SO_4-Lösung (1.5 mL) wird mit Aceton versetzt (1.5 mL) und das Gemisch unter Rühren auf 50° erwärmt. Nach Beendigung der Reaktion (4–6 h, D.C.-Kontrolle) wird mit Dowex 1-X8 (OH^-) Anionenaustauscher neutralisiert und die Lösung filtriert. Es werden die flüchtigen Bestandteile *in vacuo* abdestilliert, das anfallende Produkt in Methanol (5 mL)

gelöst und in Gegenwart einer katalytischen Menge PtO_2 unter Normaldruck für 24 h hydriert. Anschließend wird die Lösung über Celite abfiltriert, das Methanol *in vacuo* abdestilliert und **9** (115 mg, 93%) als α,β-Gemisch (2:1) gewonnen; ^{1}H-N.m.r. (400 MHz, CD_3OD) (α-D Anomer): δ 1.65–1.95 (m, 2 H, $CH_2CH_2NH_2$), 1.98 (s, 3 H, CH_3CONH), 2.93–4.02 (m, übrige H); (β-D Anomer) charakteristische Signale): δ 1.99 (s, 3 H, CH_3CONH).

Anal. (als Pentaacetat): Ber. für $C_{18}H_{28}N_2O_9$: *m/z* 416.1794 (M^+). Gef.: *m/z* 416.1788.

*3-[2-(2-Acetamido-2-desoxy-α,β-D-glucopyranosyl)ethyl]-1-*p*-nitrophenyltriazen* (**10**). — Zu einer Lösung von Verbindung **9** (60.5 mg, 0.244 mmol) in eiskaltem Wasser (1 mL) wird *p*-Nitrophenyldiazoniumtetrafluoroborat (27 mg, 0.122 mmol) gegeben und die Reaktionsmischung erst für 10 min bei 20°, dann für 20 min bei 0° (Eisbad) gerührt. Anschließend wird eiskaltes Wasser (2 mL) zugefügt und die unlöslichen Feststoffe abfiltriert. Die hellgelbe Reaktionslösung wird dreimal (je 3 mL) mit eiskaltem Ether (H_2O-gesättigt) ausgeschüttelt, um das entstandene Diazoniumhydroxid zu entfernen. Die etherische Phase wird verworfen und die wäßrige noch dreimal (je 1 mL) mit eiskaltem Butanol ausgeschüttelt. Die butanolischen Phasen werden vereinigt und lyophylisiert; Ausb. 29 mg (30%). Das Produkt wird sofort in dest. Wasser gelöst und so für die enzymatischen Experimente verwendet; ^{1}H-n.m.r. (D_2O, 25°; charakteristische Signale): δ 7.48 (m), 7.78 (m), 8.24 (m), 8.74 (m), 8.90 (m).

DANK

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INTRAMOLECULAR *C*-ARYLATION OF 2,3,5-TRI-*O*-BENZYL- AND 2,3,5-TRI-*O*-(3-METHYLBENZYL)-PENTOFURANOSE DERIVATIVES*

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ABSTRACT

Upon treatment with tin(IV) chloride, 1-*O*-acetyl-2,3,5-tri-*O*-benzyl- and 1-*O*-acetyl-2,3,5-tri-*O*-(3-methylbenzyl)pentofuranose (D-*ribo*, L-*arabino*) undergo intramolecular Friedel–Crafts alkylation of the aromatic substituent at O-2 to give unusual internal *C*-glycosyl compounds (isochroman derivatives) in high yield. The final products are also partially debenzylated at O-3 or O-5 (up to 25%) under these conditions. By contrast, the corresponding methyl glycosides are poor substrates for the intramolecular *C*-arylation reaction, as methyl 2,3,5-tri-*O*-(3-methylbenzyl)-β-D-ribofuranoside was found to give preponderantly methyl 3,5-di-*O*-(3-methylbenzyl)-α-D-ribofuranoside (**11**) (49%), and the *C*-arylation product in 30% yield only in the presence of the same Lewis acid. The competitive formation of **11** is thought to be due to the anomerization of the substrate leading to a tin(IV) complex coordinated with O-1 and O-2, which promoted the cleavage of the benzyl group at O-2. These reactions provide a novel and efficient *C*-arylation method and suggest a new approach to selectively protected D-ribofuranose derivatives. Evidence for the uncommon *C*-arylated structure of the new products was gained from their ^{1}H- and ^{13}C(APT)-n.m.r. spectra.

INTRODUCTION

As they contain both a reactive aromatic ring and an electrophilic center, 2-*O*-benzylated glycosides and analogs constitute potential substrates for intramolecular Friedel–Crafts reactions. Surprisingly, although benzylated glycosyl carboxylates[3] and halides[4] have been frequently used in *O*- and *C*-glycosylation reactions catalyzed by hard Lewis acids, such a behavior has never been observed. In the course of our investigations on the synthesis of novel *C*-glycosyl compounds, we have recently uncovered[1] the ability of benzylated glycofuranosyl acetates to

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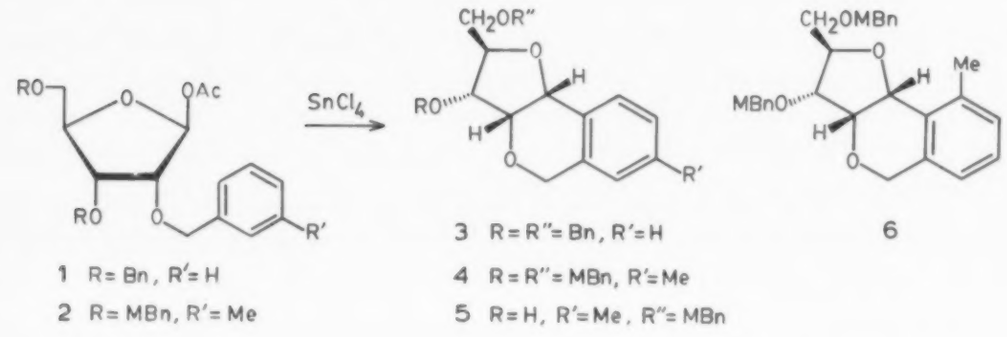
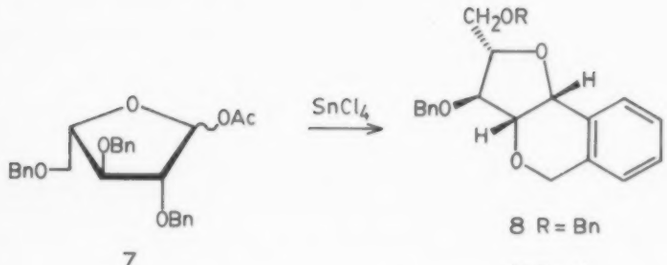
undergo readily intramolecular *C*-arylation upon reaction with a Friedel–Crafts-type catalyst. Further unexpected results were obtained[2] when D-ribofuranose derivatives bearing three 3-methoxybenzyl substituents were treated with tin(IV) chloride, as they underwent an unprecedented intramolecular double *C*-arylation resulting from the internal alkylation of the groups at O-2 and O-3.

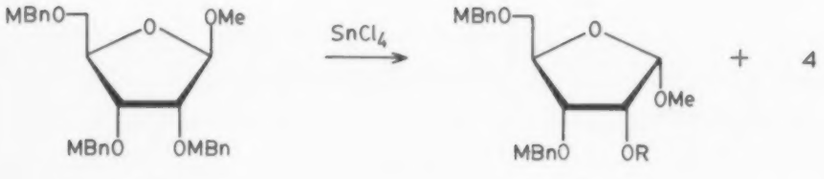
In order to determine the feasibility of the intramolecular *C*-arylation starting from the more readily accessible methyl glycosides, we examined the tin(IV) chloride-mediated reaction of a methyl glycoside containing activated benzyl groups, namely methyl 2,3,5-tri-*O*-(3-methylbenzyl)-*β*-D-ribofuranoside (**10**), as well as that of the corresponding 1-*O*-acetylglycosyl compound **2**. We wish to describe, in this article, the full details of our investigations on benzylated and 3-methylbenzylated pentofuranose derivatives, provide evidence for the structure of the new compounds, and propose a mechanism accounting for our observations.



1 R = Bn, R' = H
2 R = MBn, R' = Me
3 R = R" = Bn, R' = H
4 R = R" = MBn, R' = Me
5 R = H, R' = Me, R" = MBn
6



7
8 R = Bn
9 R = H



10
11 R = H
12 R = Ac

MBn = 3-Methylbenzyl

RESULTS AND DISCUSSION

Treatment of 1-*O*-acetyl-2,3,5-tri-*O*-benzyl-β-D-ribofuranose (**1**) and -α,β-L-arabinofuranose (**7**) with tin(IV) chloride afforded, in 1–2 h at room temperature, the corresponding *C*-arylation products **3** and **8** in yields of 46 and 60%*, respectively; both reactions also gave a small amount of a more polar product (t.l.c.) that was isolated (21%) in the case of the *arabino* series and identified as the 5-*O*-debenzylated analog of **8**, compound **9**. Under the same conditions, 1-*O*-acetyl-2,3,5-tri-*O*-(3-methylbenzyl)-β-D-ribofuranose (**2**) led preponderantly to a product resulting, as expected, from the intramolecular alkylation of the benzyl group in *para* position with respect to the activating substituent (compound **4**, 55%), as well as to a trace (7.7%) of the isomeric *ortho*-alkylation product **6**. In addition, compound **5**, which arose from the debenzylation of the final product at O-3 in this case, was isolated in a yield of 11%. The position of the free hydroxyl function in **5** and **9** was revealed by the presence of $HOCH_{(2)}$ couplings in the ^{1}H-n.m.r. spectrum for a solution in (^{2}H)chloroform.

Thus, as shown by the total yield of *C*-glycosylated products in each case, the intramolecular Friedel–Crafts reaction of benzylated 1-*O*-acetyl-glycofuranoses is a convenient process leading specifically to *cis*-substituted isochroman derivatives and, thereby, providing an efficient synthetic method for this heterocyclic system[5]. This process is much easier than the corresponding intermolecular *C*-glycosylation of aromatic or heteroaromatic compounds, which have been successful only with highly electron-rich systems, such as anisole[6], di- or tri-methoxybenzene[6–10], ferrocene[6], furane[6], and indole[11]; the Lewis acid-catalyzed *C*-glucosylation of benzene itself and toluene required drastic conditions and led to mixtures of products[12]. It is interesting to note that 2,3,5-tri-*O*-benzyl-D-ribofuranosyl bromide reacted[11] preferentially by an intermolecular process when treated with indole derivatives and silver oxide, albeit in low yield (16%).

By contrast with that of the furanoses, the reaction of benzylated 1-*O*-acetyl-hexopyranoses with the same Lewis acid gave a mixture of several partially *O*-debenzylated products, possibly including *C*-glycosyl derivatives, both in the *gluco* and in the *manno* series[13]. Further investigations are in progress to elucidate the behavior of these important substrates.

The *C*-glycosylated structure of the final products (**3, 4,** and **8**) is supported by the absence of signals of functional groups in their i.r. spectrum and by their lack of reactivity toward potassium permanganate, which rules out the isomeric unsaturated structure resulting from elimination of acetic acid (1,4-anhydro-2,3,5-tri-*O*-benzyl-D-*erythro*-pent-1-enitol[14,15])**. Many features of their ^{1}H-n.m.r. spectra

*All yields are after isolation by column chromatography, or crystallization, or both.

**See comments in ref. 1. The data reported for this compound in refs. 14 and 15 are different and therefore subject to caution.

point toward their unusual constitution (a substituted *cis*-3,3a,5,9b-tetrahydro-2*H*-furo[3,2-*c*][2]benzopyran system): the number of aromatic protons, the chemical shift of H-1 (H-9b in polycyclic system) (δ 4.68–4.82), and the magnitude of the geminal coupling constants of the benzyl methylene groups. The protons at C-5 of the polycyclic system exhibited indeed a $|J_{gem}|$ value consistently larger (14.5–15.1 Hz) than that usually found in *O*-benzyl groups (12 Hz), a difference attributable to the change of the average position of the CH_2 group with respect to the aromatic π-system in the cyclic structure[16]. Furthermore, the substitution pattern of the tri-substituted aromatic ring in compounds **4–6** was revealed by the multiplicity of the isolated signals of H-6 (s in **4** and **5**, d in **6**) and H-9 (d in **4** and **5**, absent in **6**) (polycyclic system numbering) in the ^{1}H-n.m.r. spectra. Finally, the coupling constants for the D-ribofuranose component indicated clearly a conformation close to $^3T_2$ or ^3E for the 5-membered ring, a typical conformation for 1,2-*cis*-fused bicyclic pentofuranoid systems[17] and, thus, rule out a structure which would have resulted from the intramolecular alkylation of the benzyl group at O-5.

The most convincing evidence for the structure of the *C*-arylated products was provided by the ^{13}C-n.m.r. spectra; an APT experiment performed on compounds **3** (see Fig. 1), **4**, and **8** revealed indeed the presence of *four aromatic quater-*

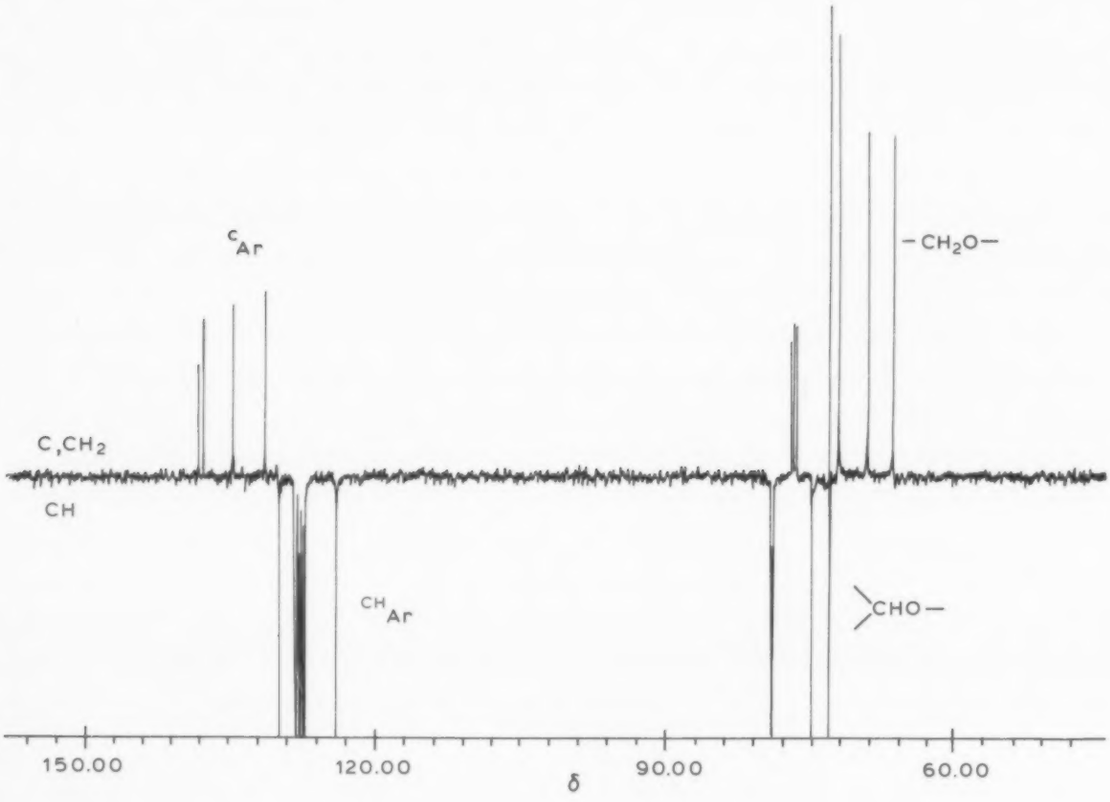
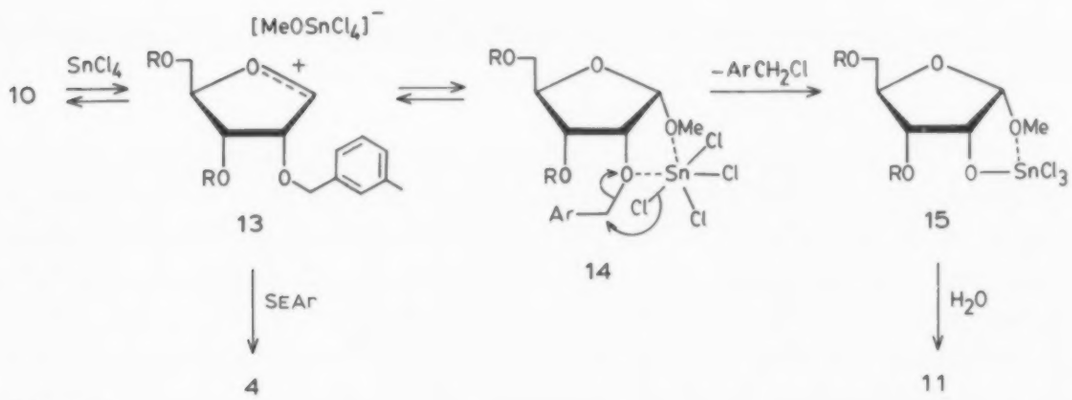


Fig. 1. ^{13}C-N.m.r. spectrum at 125.76 MHz of compound **3** (APT-experiment).

nary carbons (seven in the case of **4**), which demonstrated the existence of an additional alkylation site on one of the aromatic rings; furthermore, the signal of the former anomeric carbon (C-9b) appeared at a much higher field (δ 73–80) than in a normal furanoside (C-1, δ 100–110) and, thus, confirmed the *C*-glycosylated structure of the final products.

The behavior of methyl glycoside **10** in the presence of tin(IV) chloride was found to be remarkably different from that of the corresponding 1-*O*-acetylglycose **2**; the *C*-arylated product **4** was obtained, indeed, in a yield of 30% only, the major product being methyl 3,5-di-*O*-(3-methylbenzyl)-α-D-ribofuranoside (**11**) (49%). No trace of the β-D anomer was detected. The change of chemical shift of H-2 upon acetylation allowed an unambiguous assignment of the position of the free OH group in **11**. In order to explain the selective cleavage of the group at O-2, we suggest (see Scheme 1) that compound **10** underwent a tin(IV) chloride-mediated anomerization (see ref. 18 for examples of Lewis acid-catalyzed anomerization of methyl glycosides) to the corresponding α-D anomer which forms a favorable chelate with the reagent (**14**)*, by way of an intermediate such as **13**; this intermediate also led, competitively and irreversibly, to compound **4** by an internal SEAr reaction. The tin(IV) complex in **14** activated the 2-benzyl ether function and promoted its cleavage to 3-methylbenzyl chloride and a 2-*O*-trichlorostannyl intermediate (**15**), from which **11** was formed upon hydrolytic processing.



Scheme 1.

In light of this mechanism, the behavior of the 1-*O*-acetylglycoses (**1, 2,** and **7**) can be justified by the facts that the acetoxy group is a stronger Lewis base than the methoxy group, and that the acetate ion acts as a *bidentate ligand* yielding a chelate-type complex with the reagent[20], thereby allowing the intermediate corresponding to **13** to undergo an SEAr reaction exclusively. It is not excluded that a

*This interpretation is supported by the strong affinity of tin(IV) chloride for oxygenated ligands and its high tendency to form hexacoordinated complexes[19].

glycosyl chloride might also be formed as an additional intermediate in this reaction.

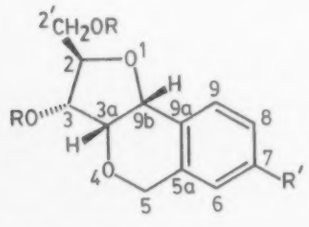
By decreasing the reactivity of the benzyl substituents towards an SEAr reaction it should be possible to achieve the 2-*O*-debenzylation of the methyl glycosides chemoselectively. Indeed, using 4-chlorobenzyl groups, we have been able to obtain exclusively the 2-*O*-debenzylated product; this very useful reaction will be described in a separate publication[21].

In conclusion, the intramolecular *C*-arylation of benzylated sugars afforded a novel method for the creation of a carbon–carbon bond between the anomeric center and an aromatic system, an unusual structural feature present in natural products such as *C*-glycosyl flavonoids and several antitumor antibiotics (nogalamycin, chromoxymycin, etc.). Because of the presence of this linkage, the synthesis of these materials is extremely difficult, and the intramolecular *C*-arylation method should provide a useful tool in this field.

EXPERIMENTAL

General methods. — Melting points were determined on a Fisher–Johns apparatus or on a Thermolyne microscope apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer model 243 automatic polarimeter for solutions in a 0.1-dm cell at 22 ±3°. I.r. spectra were recorded with a Perkin–Elmer 283B spectrophotometer. ^{1}H-N.m.r. spectra were recorded at 60, 300, 360, or 400 MHz, and ^{13}C-n.m.r. spectra at 125.76 MHz, for solutions in (^{2}H)chloroform with tetramethylsilane as the internal standard; chemical shifts (δ) are given downfield from the signal of Me_4Si. Chemical shifts and coupling constants were obtained from first-order analyses of the ^{1}H-n.m.r. spectra. ^{13}C-N.m.r. spectra were recorded in the APT-mode; (+) and (−) are used to indicate positive (quaternary and methylene) and negative (methine and methyl) amplitude of the signals. Mass spectra were recorded on a g.l.c.–m.s. HP-5995 system using the direct inlet probe.

Analytical t.l.c. was performed on precoated glass-plates with Merck silica gel 60 F-254 as the adsorbent (layer thickness 0.25 mm). The developed plates were air dried and irradiated with u.v. light, or sprayed with a solution of ammonium phosphomolybdate[22] (or both), and heated at 120–140°. Column chromatography was performed on silica gel 60 (70–230 mesh) and flash chromatography[23] on silica gel 60 (230–400 mesh). The following solvent systems (v/v) were used; (*A*) 1:3, (*B*) 1:2, (*C*) 1:1, (*D*) 2:3, (*E*) 2:1, and (*F*) 3:2 ether–hexanes. Solvents were evaporated under reduced pressure and below 40°. The *C*-arylated compounds are numbered as given in Scheme 2.



Scheme 2.

*Methyl 2,3,5-tri-*O*-(3-methylbenzyl)-β-*D*-ribofuranoside* (**10**). — Pentane-washed NaH (0.5 g, 20.8 mmol) was added to dry dimethyl sulfoxide (20 mL) and the mixture stirred for 30 min at 25°. A solution of crude methyl D-ribofuranoside[24] (β:α ~10:1) (1.0 g, 6.09 mmol) in dimethyl sulfoxide (5 mL) was then carefully added, followed by 3-methylbenzyl chloride (2.8 mL, 21 mmol). After 2 h at 25°, the excess of reagent was removed by addition of methanol (1 mL), and the mixture poured into a separatory funnel containing ether (100 mL) and ice (50 g). The organic phase was separated, the aqueous phase washed with ether (50 mL), and the combined organic phases dried (Na_2SO_4) and evaporated. The syrupy residue was submitted to flash chromatography (*A*) which afforded **10** (1.64 g, 57%); an analytical sample was obtained by column chromatography (*B*); syrup, $[\alpha]_D^{20}$ +26.5° (*c* 1.2, chloroform); t.l.c. (*C*) R_F 0.53; ν_{max}^{film} 3020, 2915, 2860, 1610, 1593, 1490, 1460, 1358, 1157, 1105, 1075, 1030, 945, 775, 740, and 690 cm^{-1}; ^{1}H-n.m.r. (60 MHz): δ 2.37 (s, 9 H, 3 $ArCH_3$), 3.37 (s, 3 H_2, OCH_3), 3.63 (m, 2 H, H-5A,5B), 3.90 (dd, 1 H, $J_{1,2}$ 1.0, $J_{2,3}$ 4.5 Hz, H-2), 4.08 (dd, 1 H, $J_{3,4}$ 6.8 Hz, H-3), 4.38 (m, 1 H, H-4), 4.55, 4.62 and 4.68 (3 s, 3 H_2, 3 $ArCH_2$), 5.00 (br. s, 1 H, H-1), and 7.28 (br. s, 12 H, 3 $MeC_6H_4CH_2$); m.s.: *m/z* 105 (100%), 79 (4), 77 (3), 103 (3), 135 (3), 209 (3), 91 (2), 143 (2), 281 (2), . . ., 339 (0.2, $[M - C_8H_9 - CH_3OH]^+$), and 371 (<0.1, $[M - C_8H_9]^+$).

Anal. Calc. for $C_{30}H_{36}O_5$ (476.61): C, 75.60; H, 7.61. Found: C, 75.58; H, 7.63.

*1-*O*-Acetyl-2,3,5-tri-*O*-(3-methylbenzyl)-β-*D*-ribofuranose* (**2**). — A solution of **10** (1.0 g, 2.1 mmol) in a mixture of peroxide-free 1,4-dioxane (25 mL) and M aqueous HCl (10 mL) was heated at reflux for 3 h. The mixture was cooled down and made neutral with M aqueous NaOH. The organic solvent was evaporated under reduced pressure, the remaining mixture extracted with chloroform (25 mL), the organic phase washed with saturated aqueous $NaHCO_3$ (10 mL), then with water (10 mL), dried (Na_2SO_4), and evaporated. The syrupy residue was submitted to flash chromatography (*C*) which afforded pure 2,3,5-tri-*O*-(3-methylbenzyl)-D-ribofuranose (0.74 g, 76%), t.l.c. (*C*) R_F 0.26; ν_{max}^{film} 3410 cm^{-1} (OH). Acetylation of this material with acetic anhydride (2 mL) in pyridine (6 mL) afforded, after standard processing, a quantitative yield of 1-*O*-acetyl derivative **2**. An analytical sample was obtained by column chromatography (*B*) and crystallization from ether–hexanes; m.p. 39–41.5°, $[\alpha]_D^{20}$ +51° (*c* 1.2, chloroform), t.l.c. (*C*) R_F 0.44; ν_{max}^{film} 3020, 2920, 2865, 1745 (C=O), 1610, 1593, 1490, 1460, 1230, 1100, 1040, 1010, 945, 775, 747, and 690 cm^{-1}; ^{1}H-n.m.r. (60 MHz): δ 1.93 (s, 3 H, $COCH_3$), 2.35 (s, 9 H, 3 $ArCH_3$), 3.67 (m, 2 H, H-5A,5B), 3.96 (d, 1 H, $J_{1,2}$ ~0, $J_{2,3}$ 4.2 Hz, H-2), 4.16 (dd, 1 H, $J_{3,4}$ 7.5 Hz, H-3), ~4.37 (m, 1 H, H-4), 4.50 (br. s, 2 H), 4.54 (s, 2 H) and 4.69 (AB, 2 H) (3 $ArCH_2$), 6.27 (s, 1 H, H-1), and 7.23 (m and s, 12 H, 3 $MeC_6H_4CH_2$); m.s.: *m/z* 105 (100%), 43 (14), 106 (11), 79 (5), 77 (4), 143 (4), 103 (3), 119 (3), 91 (3), 121 (2), . . ., and 339 (0.4, $[M - C_8H_9 - CH_3COOH]^+$).

Anal. Calc. for $C_{31}H_{36}O_6$ (504.62): C, 73.79; H, 7.19. Found: C, 73.61; H, 7.03.

(2R,3R,3aS,9bR)-3-Benzyloxy-2-benzyloxymethyl-3,3a,5,9b-tetrahydro-2H-furo[3,2-c][2]benzopyran (**3**). — To a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzyl-β-D-ribofuranose[25] (**1**) (209.5 mg, 0.45 mmol) (prepared by acetylation of 2,3,5-tri-*O*-benzyl-D-ribofuranose[24,26]) in dry dichloromethane (4 mL), was added under N_2, a 10% (v/v) solution (0.65 mL, 0.56 mmol) of $SnCl_4$ in dichloromethane, and the mixture stirred for 1.5 h at room temperature. The reagent was then removed by the addition, at 0°, of saturated aqueous $NaHCO_3$. Dichloromethane (10 mL) was added, the organic phase separated, washed with water (5 mL), dried (Na_2SO_4), and evaporated. The residue was submitted to column chromatography (*D*) which afforded crystalline **3** (84 mg, 46%). A sample was recrystallized from chloroform–ether–hexane, m.p. 111–112°, $[\alpha]_D^{20}$ +80° (*c* 0.87, chloroform); t.l.c. (*C*) R_F 0.37; ν_{max}^{KBr} 3025, 2950, 2915, 2890, 2870, 2790, 1610, 1497, 1457, 1350, 1125, 1085, 1070, 1058, 1043, 740, and 693 cm^{-1}; ^{1}H-n.m.r. (300 MHz): δ 3.54 (dd, 1 H, $J_{2,2'A}$ 3.7, $J_{2'A,2'B}$ 11.0 Hz, H-2′A), 3.70 (dd, 1 H, $J_{2,2'B}$ 2.2 Hz, H-2′B), 4.08 (dd, 1 H, $J_{3,3a}$ 3.9, $J_{3a,9b}$ 2.9 Hz, H-3a), 4.19 (ddd, 1 H, $J_{2,3}$ 8.8 Hz, H-2), 4.27 (dd, 1 H, H-3), 4.45 (d, 1 H, *J* 12 Hz), 4.57 (d, 1 H), and 4.57 (AB, 2 H, *J* 12 Hz, 2 $OCH_2C_6H_5$), 4.68 (d, 1 H, H-9b), 4.70 (d, 1 H, $J_{5A,5B}$ 15.1 Hz, H-5A), 4.85 (d, 1 H, H-5B), 7.00 (m, 1 H), 7.15–7.35 (several m, 12 H), and 7.38 (m, 1 H) (2 $OCH_2C_6H_5$, H-6–9); ^{13}C-n.m.r.: δ 66.78, 69.41, 72.35, and 73.30 [(+), C-2′, C-5, 2 $OCH_2C_6H_5$], 73.22, 75.08, 79.09, and 79.25 [(−), C-2,3,3a,9b], 124.00 [(−), C-9], 127.19–128.19 and 129.85 [(−), C-6–8, C-2–6 of 2 $OCH_2C_6H_5$], 131.36, 134.70 [(+), C-9a,5a], 137.77, and 138.30 [(+), C-1 of 2 $OCH_2C_6H_5$]; m.s.: *m/z* 91 (100%), 131 (19), 65 (9), 92 (8), 132 (7), 105 (6), 43 (5), 104 (4), 77 (4), 133 (4), . . ., 311 (2, $[M - C_7H_7]^+$), and 402 (0.1, $[M]^+$).

Anal. Calc. for $C_{26}H_{26}O_4$ (402.49): C, 77.59; H, 6.51. Found: C, 77.53; H, 6.82.

Reaction of **2** *with* $SnCl_4$. — 1-*O*-Acetylribose **2** (250 mg, 0.495 mmol) was treated with $SnCl_4$ (1 equiv.) as described for the preparation of **3**. Separation of the processed reaction mixture by column chromatography (solvent *B*, then *C* after elution of major product) afforded, in order of elution, pure **6** (17 mg, 7.7%), **4** (120 mg, 55%), and **5** (19 mg, 11.3%).

(2R,3R,3aS,9bR)-3,3a,5,9b-Tetrahydro-7-methyl-3-(3-methylbenzyloxy)-2-(3-methylbenzyloxymethyl)-2H-furo[3,2-c][2]benzopyran (**4**). — Syrup, $[\alpha]_D^{20}$ +70° (*c* 1.2, chloroform), t.l.c. (*C*) R_F 0.39; ν_{max}^{film} 3020, 2910, 2860, 1610, 1450, 1357, 1157, 1115, 1063, 780, and 692 cm^{-1}; ^{1}H-n.m.r. (360 MHz): δ 2.32, 2.338 and 2.342 (3 s, 9 H, 3 $ArCH_3$), 3.61 (dd, 1 H, $J_{2,2'A}$ 3.3, $J_{2'A,2'B}$ 11.1 Hz, H-2′A), 3.77 (dd, 1 H, $J_{2,2'B}$ 2.1 Hz, H-2′B), 4.11 (t, 1 H, $J_{3,3a}$ 4.1, $J_{3a,9b}$ 2.9 Hz, H-3a), 4.26 (td, 1 H, $J_{2,3}$ 8.6 Hz, H-2), 4.31 (dd, 1 H, H-3), 4.49 (d, 1 H, *J* 11.9 Hz) and 4.60 (d, 1 H), 4.59 (d, 1 H, *J* 11.9 Hz) and 4.72 (d, 1 H) (2 AB, 2 OCH_2Ar), 4.58 (d, 1 H, $J_{5A,5B}$ 14.7 Hz, H-5A), 4.73 (d, 1 H, H-9b), 4.88 (d, 1 H, H-5B), 6.89 (s, 1 H, H-6), 7.08–7.27 (several m, 9 H, H-8, 2 $MeC_6H_4CH_2$), and 7.33 (d, 1 H, $J_{8,9}$ 7.8 Hz, H-9); ^{13}C-n.m.r.: δ 21.16, 21.29 [(−), 3 $ArCH_3$], 66.83, 69.46, 72.45 and 73.40 [(+), C-2′, C-5, 2 OCH_2Ar], 73.12, 75.21, 79.15 and 79.25 [(−), C-2,3,3a,9b], 124.48, 124.64,

and 124.94 [(−), C-9, C-6 of 2 $CH_2C_6H_4Me$], 128.03–128.62 and 129.77 [(−), C-6–C-8, C-2 and C-4,5 of 2 $CH_2C_6H_4Me$], 128.49, 134.60 [(+), C-9a,5a], 137.74 (2 C), 137.82, 137.95, and 138.28 [(+), C-1 and C-3 of 2 $CH_2C_6H_4Me$]; m.s.: *m/z* 105 (100%), 145 (31), 146 (11), 106 (10), 119 (7), 79 (6), 147 (5), 187 (5), 339 (5, $[M - C_8H_9]^+$), 175 (3), . . ., and 444 (1, $[M]^+$).

Anal. Calc. for $C_{29}H_{32}O_4$ (444.57): C, 78.34; H, 7.26. Found: C, 78.40; H, 7.36.

*(2*R*,3*R*,3a*S*,9b*R*)-3,3a,5,9b-Tetrahydro-3-hydroxy-7-methyl-2-(3-methylbenzyloxymethyl)-2*H*-furo[3,2-*c*][2]benzopyran* (**5**). — Recrystallized from ether–hexane, m.p. 82.5–84°, $[\alpha]_D^{20}$ 0° (*c* 0.7, chloroform); t.l.c. (*C*) R_F 0.14; ν_{max}^{KBr} 3370 (OH), 3020, 2920, 2860, 1615, 1433, 1370, 1130, 1092, 1065, 990, 788, 695, and 660 cm^{-1}; ^{1}H-n.m.r. (360 MHz): δ 2.33 and 2.35 (2 s, 6 H, 2 $ArCH_3$), 2.67 (br. d, 1 H, $J_{3,OH}$ ~10 Hz, HO-3), 3.69 (dd, 1 H, $J_{2,2'A}$ 4.1, $J_{2'A,2'B}$ 10.7 Hz, H-2′A), 3.78 (dd, 1 H, $J_{2,2'B}$ 2.9 Hz, H-2′B), 4.01 (ddd, 1 H, $J_{2,3}$ 8.5 Hz, H-2), 4.19 (dd, 1 H, $J_{3,3a}$ 4.5, $J_{3a,9b}$ 3.3 Hz, H-3a), 4.47 (br. td, 1 H, H-3), 4.60 (AB, 2 H, *J* 12 Hz, OCH_2Ar-2′), 4.65 (d, 1 H, $J_{5A,5B}$ 14.7 Hz, H-5A), 4.82 (d, 1 H, H-9b), 4.84 (d, 1 H, H-5B), 6.89 (s, 1 H, H-6), 7.08–7.19 (m, 4 H, $MeC_6H_4CH_2$), 7.23 (d, 1 H, $J_{8,9}$ 7.8 Hz, H-8), and 7.37 (d, 1 H, H-9); m.s.: *m/z* 105 (100%), 131 (51), 175 (47), 146 (45), 147 (40), 145 (38), 119 (34), 159 (26), 91 (26), 117 (23), . . ., 235 (7.6, $[M - C_8H_9]^+$), and 340 (2.6, $[M]^+$).

Anal. Calc. for $C_{21}H_{24}O_4$ (340.42): C, 74.09; H, 7.11. Found: C, 73.63; H, 7.06.

*(2*R*,3*R*,3a*S*,9b*R*)-3,3a,5,9b-Tetrahydro-9-methyl-3-(3-methylbenzyloxy)-2-(3-methylbenzyloxymethyl)-2*H*-furo[3,2-*c*][2]benzopyran* (**6**). — Syrup, $[\alpha]_D^{20}$ +54° (*c* 0.52, chloroform); t.l.c. (*C*) R_F 0.46; ν_{max}^{KBr} 3020, 2915, 2860, 1605, 1465, 1345, 1155, 1115, 1080, 1060, 920, 770, 730, and 690 cm^{-1}; ^{1}H-n.m.r. (360 MHz): δ 2.35 (s, 6 H) and 2.43 (s, 3 H) (3 $ArCH_3$), 3.63 (dd, 1 H, $J_{2,2'A}$ ~3.5, $J_{2'A,2'B}$ ~10.5 Hz, H-2′A), 3.77 (dd, 1 H, $J_{2,2'B}$ ~2 Hz, H-2′B), 4.08 (dd, $J_{3,3a}$ ~3.5, $J_{3a,9b}$ ~2 Hz, H-3a), 4.30 (m, 1 H, $J_{2,3}$ ~8 Hz, H-2), 4.36 (dd, 1 H, H-3), 4.58 (AB, 2 H, *J* ~12 Hz, OCH_2Ar), 4.62 (d, 1 H, *J* ~12 Hz), and 4.75 (d, 1 H) (AB, OCH_2Ar), 4.62 (d, 1 H, H-5A), 4.80 (d, 1 H, H-9b), 4.93 (d, 1 H, $J_{5A,5B}$ ~15 Hz, H-5B), 6.90 (d, 1 H, $J_{6,7}$ 7.4 Hz, H-6), and 7.08–7.23 (several m, 10 H, H-7,8, 2 $MeC_6H_4CH_2$); m.s.: *m/z* 105 (100%), 145 (29), 106 (10), 146 (9), 119 (8), 79 (8), 77 (8), 91 (6), 103 (6), 118 (5), . . ., 339 (0.6, $[M - C_8H_9]^+$), 444 (0.1, $[M]^+$).

Anal. Calc. for $C_{29}H_{32}O_4$ (444.57): C, 78.34; H, 7.26. Found: C, 78.39; H, 7.36.

*(2*S*,3*S*,3a*S*,9b*R*)-3-Benzyloxy-2-benzyloxymethyl-3,3a,5,9b-tetrahydro-2*H*-furo[3,2-*c*][2]benzopyran* (**8**). — 1-*O*-Acetyl-2,3,5-tri-*O*-benzyl-L-arabinofuranose[27] (**7**) (α/β ~3:1) (300 mg, 0.65 mmol) was treated with $SnCl_4$ (1 equiv.) as described for the preparation of **3**. The processed reaction mixture was submitted to column chromatography (solvent *B*, then *C*) which afforded 157 mg (60%) of pure **8** and 43 mg (21%) of its 5-*O*-debenzylated analog (**9**). Compound **8**: syrup, $[\alpha]_D^{20}$ −5.4 ±1° (*c* 1.1, chloroform); t.l.c. (*C*) R_F 0.59; ν_{max}^{film} 3030, 2900, 2860, 1605, 1587, 1496,

1454, 1370, 1205, 1090 (br.), 740, and 693 cm^{-1}; ^{1}H-n.m.r. (400 MHz): δ 3.61 (dd, 1 H, $J_{2,2'A}$ 6.0, $J_{2'A,2'B}$ 10.0 Hz, H-2'A), 3.65 (dd, 1 H, $J_{2,2'B}$ 6.0 Hz, H-2'B), 4.00 (d, 1 H, $J_{3,3a}$ <0.5, $J_{2,3}$ 4.0 Hz, H-3), 4.21 (d overlapping br. q, 2 H, $J_{3a,9b}$ 3.0 Hz, H-3a, H-2), 4.54 (AB, 2 H, *J* 12.0 Hz, $OCH_2C_6H_5$), 4.64 (d, 1 H, $J_{5A,5B}$ 14.5 Hz, H-5A), 4.65 (AB, 2 H, *J* 12.0 Hz, $OCH_2C_6H_5$), 4.75 (d, 1 H, H-9b), 4.76 (d, 1 H, H-5B), 7.05 (m, 1 H), 7.23–7.36 (several m, 12 H), and 7.48 (m, 1 H) (H-6–9, 2 $CH_2C_6H_5$); ^{13}C-n.m.r.: δ 67.17, 70.61, 72.02, and 73.30 [(+), C-2', C-5, 2 $OCH_2C_6H_5$], 74.11, 81.34, 82.98, and 86.71 [(−), C-2,3,3a,9b], 124.08 [(−), C-9], 127.22–128.32 and 130.31 [(−), C-6–8, C-2–6 of 2 $OCH_2C_6H_5$], 130.44, 134.88 [(+), C-9a,5a], 137.68, and 138.15 [(+), C-1 of 2 $OCH_2C_6H_5$]; s.m.: *m/z* 91 (100%), 131 (17), 65 (10), 105 (10), 132 (9), 92 (9), 77 (7), 145 (6), 133 (5), 104 (5), . . ., 311 (0.4, $[M - C_7H_7]^+$), and 402 (0.3, $[M]^+$).

Anal. Calc. for $C_{26}H_{26}O_4$ (402.49): C, 77.59; H, 6.51. Found: C, 77.15; H, 6.57.

(2S,3S,3aS,9bR)-3-Benzyloxy-3,3a,5,9b-tetrahydro-2-hydroxymethyl-2H-furo[3,2-c][2]benzopyran (**9**). — Recrystallized from ether–hexane, m.p. 72–73°, $[\alpha]_D^{20}$ −51° (*c* 0.53, chloroform); t.l.c. (*C*) R_F 0.23; ν_{max}^{film} 3460 (OH), 3030, 2860, 1605, 1590, 1495, 1455, 1370, 1205, 1090, 1050 (br.), 875, 802, 740, and 695 cm^{-1}; ^{1}H-n.m.r. (400 MHz): 2.11 (br. m, 1 H, HO-2'), 3.71 (br. ddd, 1 H, $J_{2,2'A}$ 4.5, $J_{2'A,OH}$ 6.5, $J_{2'A,2'B}$ 11.5 Hz, H-2'A), 3.85 (br. dt, 1 H, $J_{2,2'B}$ 3, $J_{2'B,OH}$ 3 Hz, H-2'B), 4.10 (d, 1 H, $J_{2,3}$ 4.0, $J_{3,3a}$ <0.5 Hz, H-3), 4.16 (br. q, 1 H, H-2), 4.21 (d, 1 H, $J_{3a,9b}$ 2.8 Hz, H-3a), 4.65 (d, 1 H, *J* 11.8 Hz) and 4.72 (d, 1 H) (AB, $OCH_2C_6H_5$), 4.69 (d, 1 H, $J_{5A,5B}$ 15.0 Hz, H-5A), 4.78 (d, 1 H, H-9b), 4.81 (d, 1 H, H-5B), 7.08 (m, 1 H), 7.28–7.40 (several m and d, 7 H), and 7.46 (m, 1 H) (H-6–9, $CH_2C_6H_5$); m.s.: *m/z* 91 (100), 131 (74), 132 (27), 105 (18), 133 (14), 65 (11), 104 (10), 92 (9), 103 (8), 77 (8), . . ., 221 (0.2 $[M - C_7H_7]^+$), and 312 (0.1, $[M]^+$).

Anal. Calc. for $C_{19}H_{20}O_4$ (312.37): C, 73.05; H, 6.45. Found: C, 71.89 (three samples); H, 6.62.

Methyl 3,5-di-O-(3-methylbenzyl)-α-D-ribofuranoside (**11**). — Methyl 2,3,5-tri-*O*-(3-methylbenzyl)-β-D-ribofuranoside (**10**) (300 mg, 0.63 mmol) was treated with $SnCl_4$ (1 equiv.) as described for the preparation of **3**. The processed mixture was submitted to column chromatography (solvent *B*, changed to *D*, then to *C*) which afforded, in order of elution, an unidentified impurity [6.8 mg; R_F (*C*) 0.51], compound **4** (85 mg, 30%), and compound **11** (115 mg, 49%); an analytical sample of **11** was obtained by column chromatography (*F*), syrup, $[\alpha]_D^{20}$ +108° (*c* 1.48, chloroform); t.l.c. (*C*) R_F 0.21; ν_{max}^{film} 3550 (OH), 3020, 2920, 2860, 1607, 1590, 1455, 1413, 1355, 1090, 1030, 780, 740, and 690 cm^{-1}; ^{1}H-n.m.r. (400 MHz): δ 2.32 and 2.35 (2 s, 6 H, 2 $ArCH_3$), 2.97 (br., 1 H, HO-2), 3.38 (dd, 1 H, $J_{4,5A}$ 4.5, $J_{5A,5B}$ 10.5 Hz, H-5A), 3.46 (dd, 1 H, $J_{4,5B}$ 4.0 Hz, H-5B), 3.48 (s, 3 H, OCH_3), 3.79 (dd, 1 H, $J_{2,3}$ 7.0, $J_{3,4}$ 3.1 Hz, H-3), 4.12 (br., 1 H, H-2), 4.17 (q, 1 H, H-4), 4.46 (AB, 2 H, *J* 12.0 Hz), 4.55 (d, 1 H, *J* 12.0 Hz) and 4.69 (d, 1 H) (2 OCH_2Ar), 4.89 (d, 1 H, $J_{1,2}$ 4.8 Hz, H-1), 7.09 (m, 6 H), and 7.21 (m, 2 H) (2 $CH_2C_6H_4CH_3$); m.s.: *m/z* 105 (100%), 106 (15), 77 (8), 79 (8), 103 (5), 91 (4), 121 (4), 45 (3), 131 (2), 147 (2),

. . ., and 267 (0.2, $[M - C_8H_9]^+$).

Anal. Calc. for $C_{22}H_{28}O_5$ (372.46): C, 70.95; H, 7.58. Found: C, 70.71; H, 7.55.

Methyl 2-O-acetyl-3,5-di-O-(3-methylbenzyl)-α-D-ribofuranoside (**12**). — Compound **11** was acetylated under standard conditions; the resulting product (**12**) was purified by preparative t.l.c. (solvent *C*); syrup, t.l.c. (*E*) R_F 0.54 (note: **11** has R_F 0.51 in solvent *E*); ν_{max}^{film} 3020, 2920, 2860, 1742 (C=O), 1610, 1490, 1457, 1375, 1240, 1125, 1090, 1065, 1040 (br.), 780, 743, and 695 cm^{-1}; ^{1}H-n.m.r. (60 MHz): δ 2.28 (s, 3 H, $OCOCH_3$), 2.37 and 2.41 (2 s, 6 H, 2 $ArCH_3$), 3.54 (s and m, 5 H, OCH_3, H-5A,5B), 4.06 and 4.23 (2 m, 2 H, H-3,4), 4.52 (s, 2 H) and 4.58 (AB, 2 H, J 12 Hz) (2 OCH_2Ar), 4.95 (dd, 1 H, $J_{1,2}$ 4.5, $J_{2,3}$ 6.5 Hz, H-2), 5.16 (d, 1 H, H-1), and 7.23 (br. s, 8 H, 2 $CH_2C_6H_4Me$); m.s.: *m/z* 105 (100%), 43 (32), 106 (13), 103 (8), 79 (6), 77 (6), 191 (5), 121 (5), 135 (4), 119 (4), . . ., 309 (0.5, $[M - C_8H_9]^+$), and 382 (0.5, $[M - CH_3OH]^+$).

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STEREOSELECTIVE SYNTHESIS OF 3-(D-GLYCOPYRANOSYL)PROPENES BY USE OF ALLYLSILANES*

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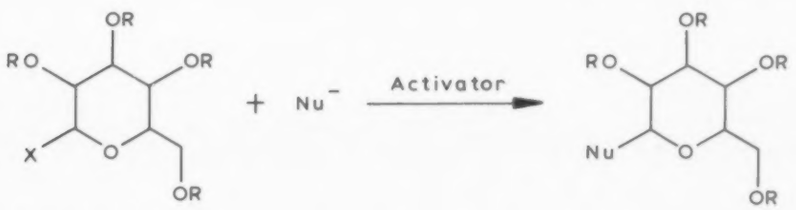
ABSTRACT

Reactions of allylsilanes with methyl pyranosides and pyranosyl chlorides proceeded very smoothly in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate and iodosilane to give the corresponding glycopyranosyl-3-propenes in highly stereoselective mode. The configuration depends upon the structure of allylsilanes. 2-Bromo-2-propenyltrimethylsilane, the lowest nucleophile among the allylsilanes used, afforded an almost pure *C*-α-D-glycosyl compound.

INTRODUCTION

Recently, much attention[1,2] has been focused on the stereoselective synthesis of pyranosyl and furanosyl compounds substituted by a functionalized alkyl group at C-1[2,3], since the products of the reaction can be used not only as chiral building blocks for the synthesis of naturally occurring compounds[4], but also as precursors to biologically active *C*-nucleosides and enzyme inhibitors, and as subunits of natural products[5]. In this direction, a number of efforts are currently being devoted to the direct formation of a carbon–carbon bond at the anomeric center of carbohydrates[6] (Scheme 1). Although the stereoselectivity depends upon the nature of the nucleophile reagent and leaving group, the activator also plays an important role in the functionalized alkylation using organosilicon reagents. We have recently



Scheme 1

*Chemistry of Organosilicon Compounds No. 218. A preliminary communication has been reported[1].
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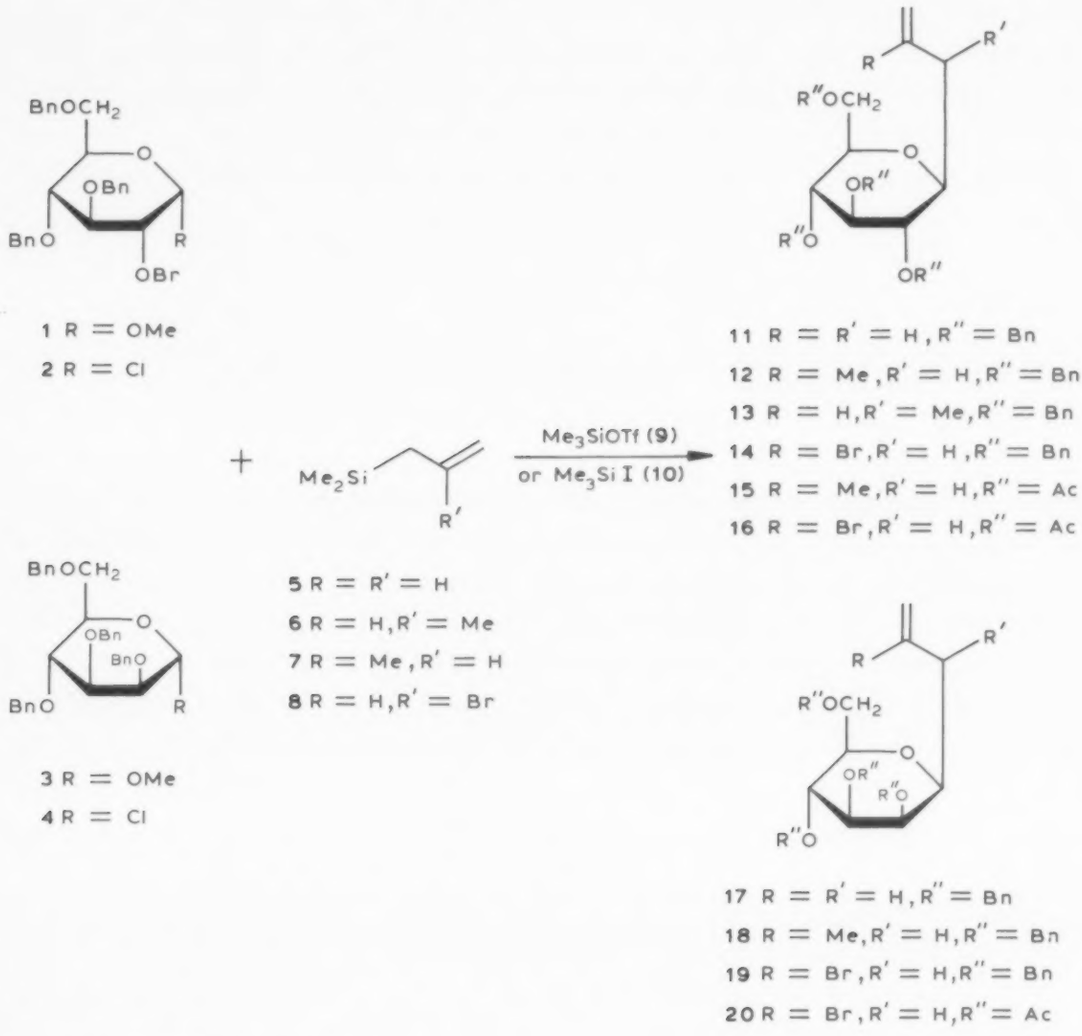
shown that α,α-diheteroatom-substituted alkanes (R^1R^2CXY; X, Y = RO, RS, R_2N, and Hal) are activated chemoselectively by trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) (**9**) and iodotrimethylsilane (**10**) to react with silyl enol ethers, ketene silyl acetals, and allylsilanes[7–10] and, especially, cyclic α-chloroethers, such as 2-chlorooxolane and 2-chlorooxane (α-chlorotetrahydropyran) display high reactivity towards allylsilanes[7,8]. Moreover, during the present work, we have found that the method can be applied to the activation of *N*-(trimethylsilylmethyl)aminomethyl ethers that function as efficient synthons for synthetically important, nonstabilized azomethine ylides[11].

We report herein the use of allylsilanes as excellent reagents for the stereoselective introduction of functionalized allyl groups at the anomeric center of carbohydrates in the presence of Me_3SiOTf (**9**) (ref. 12) and iodosilane (**10**).



RESULTS AND DISCUSSION

The reaction of 2-propenyltrimethylsilane (**5**) with methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (**1**) proceeded very smoothly in the presence of

Me_3SiOTf (**9**) in acetonitrile to give, highly stereoselectively in good yield, the α-D-glucopyranosylpropene **11**. The results and those with other allylsilanes (**6–8**) are summarized in Table I. The choice of solvent and the amount of activator are important for the success of this reaction. Thus, acetonitrile gave the most satisfactory results whereas dichloromethane, which is the most commonly used solvent for the activation of α,α-diheteroatom-substituted alkanes[7–10], was not suitable for the reaction. Although less than 10 mol of the catalyst **9** or **10**/100 mol had been sufficient previously to activate α,α-dihetereoatom-substituted alkanes, the present reaction required 20–50 mol of **9**/100 mol, presumably owing to interaction with other oxygen-functional groups in the molecule, in addition to the activation of the anomeric methoxy group. Apparently, **9** is a more efficient catalyst than **10** since the latter is known as a reagent for bond cleavage of the ether linkage[13].

Compound **11** could be obtained from the reaction of **5** with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride (**2**) catalyzed by **9** in a ratio of the two stereoisomers (α:β, 91:9) approximately similar to that obtained from **1**. In this case, even less than 20 mol of **9**/100 mol as the activator was sufficient to complete the catalytic cycle. Apparently the pyranosyl chloride was a more reactive substrate under the present allylation conditions, though the stereoselectivity was unchanged.

TABLE I

STEREOSELECTIVE SYNTHESIS OF 3-(D-GLYCOPYRANOSYL)PROPENES

Reactant	*Allylsilane*	*Conditions*		*Product*	*Yield (%)*[a]	*Ratio α- to β-D anomer*[b]
		Activator	*Time (h)*			
1	**5**	**9**	16	**11**	86	(91:9)
1	**5**	**9**	35[c]	**11**	54(23)	(91:9)
1	**5**	**9**	68[d]	**11**	Trace	(91:9)
1	**5**	[e]	48	**11**	24	(91:9)
1	**5**	**10**	27	**11**	60(22)	(91:9)
1	**6**	**9**	10	**12**	87	(86:14)
1	**7**	**9**	24	**13**	68	[f]
1	**8**	**9**	16	**14**	71	(100:0)
2	**5**	**9**	6.5	**11**	81	(91:9)
2	**5**	**10**	16	**11**	75	(91:9)
3	**5**	**9**	25	**17**	87	(100:0)
3	**5**	**10**	23	**17**	68(20)	(100:0)
3	**6**	**9**	8	**18**	81	(89:11)
3	**8**	**10**	12	**19**	45(35)	(100:0)
4	**5**	**9**	4	**17**	80	(100:0)
4	**8**	**10**	20	**19**	65	(100:0)

[a]Recovered **1** is shown in parentheses. [b]Determined by l.c. [c]20 mol% of **9**/100 mol was used. [d]The reaction was conducted in dichloromethane. [e]$BF_3 \cdot OEt_2$ was used as the activator. [f]Presumably **13** was a mixture of four diastereoisomers.

Methyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside (**3**) and 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl chloride (**4**) also reacted with allyltrimethylsilane (**5**), when very smoothly catalyzed by **9** and **10**, to afford the corresponding *C*-mannopyranosyl compound **17** with high stereoselectivity. The β-D anomer could not be detected by chromatographic and spectroscopic analysis.

From the results obtained with **1**, it could be concluded that the configuration at C-1 depends significantly upon the structure of the allylsilanes, but not upon the leaving group and the catalyst. Thus, use of 2-bromo-2-propenyltrimethylsilane[14] (**8**) resulted in a high selectivity for the α-D configuration at C-1 of **1**, whereas the β-D selectivity increased slightly with 2-methyl-2-propenyltrimethylsilane (**6**). However, it is important to point out that the β-D anomer was preponderant in all cases. The main factors controlling the configuration at C-1 in the present reaction are: (a) the stereoelectronic effect due to the lone-pair electrons of the ring oxygen atom, (b) the solvent effect, (c) the nature of the nucleophilic reagent, and (d) the steric effect.

Since the stereoselectivity of the products did not depend upon the leaving group at C-1 and the catalyst, it is reasonable to assume that the free oxonium ion **21** is the intermediate and that the nucleophilic attack of the allylsilanes **5–8** to give **22** takes place from the axial direction owing to the stereoelectronic effect[15] (Scheme 2). Moreover, undoubtedly acetonitrile accelarated the formation of the free oxonium ion (**21**) owing to the association of the solvent.

21 22

Scheme 2

The third condition for stereocontrol, the reactivity of the nucleophilic reagents, may also be considered. The α-D selectivity was decreasing gradually with the increasing nucleophilicity of the allylsilanes, in the order **6** > **5** > **8**. The nucleophilicity of **5–8** was determined by the following competitive experiment. When a mixture of a large excess of **5**, **6**, and **8** was treated with benzaldehyde dimethylacetal, catalyzed by **9**, the corresponding allylated products, **23** and **24**, were obtained in 27 and 65% yield, respectively. 2-Bromo-4-methoxy-4-phenylbutene (**25**), which might have derived from **8**, could not be detected in the reaction mixture.

5, 6, 8 → PhCHCH$_2$CH=CH$_2$ + PhCHCH$_2$C=CH$_2$ + PhCHCH$_2$C=CH$_2$

OMe		OMe	CH$_3$	OMe	Br
23	(27%)	**24**	(65%)	**25**	(0%)

The high stereoselectivity observed in the D-mannose rather than in the D-glucose series may be explained by the difference in steric hindrance of the benzyloxy group at C-2 between the two series. Thus, the reaction of both glucopyranosides and mannopyranosides with allylsilanes may be important in organic synthesis to obtain *C*-glycosylpropenes with the α-D configuration in a highly stereoselective mode.

The structures of these compounds could be readily assigned by comparing the spectral data and chromatographic behaviors with those of authentic samples. Furthermore, the configuration at C-1 was confirmed by 200-MHz, ^{1}H-n.m.r. spectroscopy. Thus, after the major stereoisomer of the tetrabenzyl derivatives **11–14** and **17–19** was isolated from the reaction mixture by l.c., it was converted into its tetraacetate by hydrogenolysis in the presence of palladium–carbon followed by acetylation with acetic anhydride and pyridine. (See Experimental for **15** and **16**). The tetraacetate was purified by t.l.c. On the basis of the $J_{1,2}$ value (~6 Hz) of the 200-MHz, ^{1}H-n.m.r. spectrum, the acetate was characterized as an α-D anomer, the $J_{1,2}$ value of the α-D anomer being smaller than that of the β-D anomer[3]. Thus, the preponderant compounds of the reaction were the α-D anomers. The ^{1}H-n.m.r. data are quite similar to those of the products obtained by the addition reaction of a pyranosyl radical to acrylonitrile which gave α-D anomers[15]. Furthermore, the values of the specific rotations of the α-D anomers were larger than those of the β-D anomers, well in accord with the values for anomers in the D-series of carbohydrates[16].

EXPERIMENTAL

Methods. — Optical rotations were measured with an Union Tec. PM-101 automatic polarimeter. I.r. spectra were recorded with a Hitachi EPI-G2 spectrometer; ^{1}H-n.m.r. spectra with a Varian T-60, EM-390, and XL-200 spectrometers; and mass spectra with a JEOL JMS-300D GC-MS spectrometer.

Materials. — Allylsilanes[17–19] (**5–8**) and other organosilicon reagents[20,21] (**9, 10**) were prepared according to methods described in the literature. 2-Propenyltrimethylsilane (**5**) had b.p. 84.5–85.5°, lit.[17] 84.9° (98 kPa); and 2-methyl-2-propenyltrimethylsilane (**6**) b.p. 108°, lit.[18] 109° (100 kPa). 2-Butenyltrimethylsilane[19] (**7**), b.p. 6°, was prepared by the fluoride ion-promoted isomerization of a mixture of 2-methyl-2-propenylsilane and 2-butenylsilanes. Trimethylsilyl trifluoromethanesulfonate (**9**), b.p. 56–60° (3.5 kPa), lit.[20] 45–47° (2.3 kPa). Iodotrimethylsilane (**10**) was prepared, by an *in situ* method[21], from hexamethyldisilane and I_2. Compounds **1–4** were prepared by procedures cited in the literature[22–24].

2-Bromo-2-propenyltrimethylsilane (**8**). — 2,3-Dibromopropene (120 g, 0.60 mol) was treated[25] with trichlorosilane (97.5 g, 0.72 mol) and triethylamine (61.0 g, 0.60 mol) in the presence of $CuCl_2$ (3.0 g, 0.03 mol) in dry ether (250 mL). The resulting ammonium salt was removed by filtration and the filtrate was methylated with an excess of methylmagnesium bromide in ether. After work-up, pure **8** (66.4 g, 0.35 mol) was obtained by distillation (57% yield), b.p. 74–75° (87 kPa); lit.[25]

64–65°) (52 kPa); $\nu_{max}^{CCl_4}$ 3060 (m), 1670 (s), 1300 (s), 1240 (m), 1210 (m), 1130 (m), and 900 cm^{-1} (s); ^{1}H-n.m.r. (60 MHz, CCl_4): δ 0.19 (s, 9 H), 2.17 (m, 2 H), and 5.19 (m, 1 H); m.s.: *m/z* 194 (6), 192 (M^+, 6), 139 (27), 74 (9), 73 (100), and 45 (10).

C-Allylation of compounds **1–4**. — *General procedure.* In a 50-mL flask, equipped with a dropping funnel and a Dimroth condenser with a drying tube, were placed, under an N_2 atmosphere, compounds **1, 2, 3**, or **4** (1.5 mmol), an allylsilane (4 mmol) and dry acetonitrile (5 mL). Trimethylsilyl triflate (**9**) (0.15 g, 0.7 mmol) was added with a syringe and the mixture was stirred at room temperature for a given period, as shown in Table I. After the solution had been cooled to 0°, pyridine (a few drops) was added, the mixture hydrolyzed with saturated $NaHCO_3$, and then extracted with ether. The organic layer was washed with water, followed by saturated NaCl, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product purified by t.l.c. on silica gel to give a mixture of stereoisomers. A similar procedure was used with iodotrimethylsilane (**10**) as a catalyst. Each stereoisomer was isolated by l.c. In general, the α-D anomer was eluted after the β-D anomer.

*3-(2,3,4,6-Tetra-*O*-benzyl-*D*-glucopyranosyl)propene*[3] (**11**). — T.l.c. (4:1 benzene–ether) R_F 0.85.

α-D Anomer. $[\alpha]_D^{21}$ +32.1° (*c* 0.97, chloroform); ν_{max}^{KBr} 3070 (w), 2910 (s), 2870 (m), 1450 (m), 1360 (m), 1100 (s), 1080 (s), 1025 (m), 995 (m), 950 (m), 910 (m), 755 (s), 735 (s), and 700 cm^{-1} (s); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 7.43–7.00 (bs, 20 H), 6.03–5.53 (m, 1 H), 5.23–4.30 (m, 9 H), 4.26–3.43 (m, 8 H), and 2.47 (br.t, 2 H, *J* 7.5 Hz).

β-D Anomer. $[\alpha]_D^{21}$ −152° (*c* 0.6, chloroform); ν_{max}^{KBr} 3065 (w), 3030 (w), 2900 (s), 2865 (s), 1445 (m), 1360 (m), 1100 (s), 1060 (s), 995 (m), 950 (m), 910 (m), 740 (s), and 700 cm^{-1} (s); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 7.40–7.00 (br.s, 20 H), 6.23–5.67 (m, 1 H), 5.23–4.37 (m, 9 H), 3.83–3.17 (m, 8 H), and 2.80–2.10 (m, 1 H).

*2-Methyl-3-(2,3,4,6-tetra-*O*-benzyl-*D*-glucopyranosyl)propene* (**12**). — T.l.c. (4:1 benzene–ether) R_F 0.85.

α-D Anomer. $[\alpha]_D^{21}$ +21.7° (*c* 2.0, chloroform); ν_{max}^{KBr} 3050 (w), 3020 (m), 2890 (s), 2845 (s), 1595 (w), 1485 (w), 1440 (m), 1350 (m), 1200 (m), 1090 (s), 900 (m), 730 (s), and 695 cm^{-1} (s); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 7.37–7.00 (br.s, 20 H), 5.00–4.07 (m, 11 H), 3.87–3.43 (m, 6 H), 2.70–2.16 (m, 2 H), and 1.73 (s, 3 H).

β-D Anomer. $[\alpha]_D^{21}$ +5.0° (*c* 0.8, chloroform); ν_{max}^{KBr} 3060 (w), 3030 (w), 2900 (m), 1490 (w), 1445 (m), 1360 (w), 1085 (bs), 735 (s), and 695 cm^{-1} (s); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 7.33–7.06 (bs, 20 H), 4.96–4.50 (m, 10 H), 3.73–3.23 (m, 7 H), and 2.70–2.00 (m, 2 H), 1.78 (s, 3 H).

Anal. Calc. for $C_{38}H_{42}O_5$: C, 78.86; H, 7.31. Found: C, 78.80; H, 7.46.

*3-(2,3,4,6-Tetra-*O*-benzyl-*D*-glucopyranosyl)butene* (**13**). — T.l.c. (2:1 hexane–ether) R_F 0.75; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 7.30–7.20 (br.s, 20 H), 6.10–5.55 (m, 1 H), 5.20–4.85 (m, 2 H), 4.70–4.55 (m, 8 H), 4.00–3.70 (m, 7 H), 2.70–3.00 (m, 1 H), and 1.15 (t, 3 H, *J* 7.0 Hz). Two stereoisomers could be separated in the ratio of ~2:3 by l.c. However, it was impossible to assign their structures

since four stereoisomers (two diastereomers of α- and β-D anomers) could be present in the reaction mixture.

2-Bromo-3-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)propene (**14**). — T.l.c. (2:1 hexane–ether) R_F 0.50; ν_{max}^{KBr} 3060 (w), 3030 (m), 2910 (m), 2850 (m), 1625 (m), 1445 (m), 1125 (s), 1090 (s), 1060 (s), 1000 (s), 900 (w), 750 (s), and 695 cm^{-1} (s); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 7.33–7.00 (br.s, 20 H), 5.63–5.52 (m, 1 H), 5.47–5.40 (m, 1 H), 4.86–4.27 (m, 9 H), 3.80–3.10 (m, 6 H), and 2.90–2.70 (m, 2 H).

Anal. Calc. for $C_{37}H_{39}BrO_5$: C, 69.05; H, 6.12; Br, 12.41. Found: C, 68.68; H, 6.26; Br, 12.67.

3-(2,3,4,6-Tetra-O-benzyl-α-D-mannopyranosyl)propene (**17**). — T.l.c. (4:1 benzene–ether) R_F 0.85; $[\alpha]_D^{21}$ −3.0° (*c* 7.0, chloroform); ν_{max}^{film} 3070 (m), 3035 (m), 1369 (m), 1205 (m), 1100 (s), 1030 (m), 915 (m), 790 (s), 760 (s), and 700 cm^{-1} (s); ^{1}H-n.m.r. (90 MHz, CCl_4): δ 7.33–7.03 (br.s, 20 H), 6.03–5.53 (m, 1 H), 5.13–4.86 (m, 2 H), 4.73–4.33 (m, 7 H), 4.10–3.53 (m, 8 H), and 2.30 (br.t, 2 H, *J* 7 Hz).

2-Methyl-3-(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)propene (**18**). — T.l.c. (2:1 hexane–ether) R_F 0.60.

α-D Anomer. $[\alpha]_D^{21}$ +4.7° (*c* 3.8, chloroform); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 7.37–6.93 (m, 20 H), 5.10–3.30 (m, 17 H), 2.32 (br.t, 2 H, *J* 6.8 Hz), and 1.70 (s, 3 H).

β-D Anomer. $[\alpha]_D^{21}$ −22° (*c* 0.9, chloroform); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 7.33–7.00 (m, 20 H), 4.83–3.56 (m, 17 H), and 2.31 (br.d, 2 H, *J* 7.5 Hz).

Anal. Calc. for $C_{38}H_{42}O_5$: C, 78.86; H, 7.31. Found: C, 78.60; H, 7.57.

2-Bromo-3-(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)propene (**19**). — T.l.c. (2:1 hexane–ether) R_F 0.45; ν_{max}^{film} 3080 (w), 3060 (w), 3020 (m), 2900 (s), 2860 (s), 1660 (w), 1450 (m), 1100 (s), 740 (s), and 700 cm^{-1} (s); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 7.40–7.07 (br.s, 20 H), 5.60–5.50 (m, 1 H), 5.43–5.38 (m, 1 H), 4.76–4.20 (m, 9 H), 4.00–5.37 (m, 6 H), and 2.67 (br.d, 2 H, *J* 7.5 Hz).

2-Methyl-1-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)propane (**15**). — Compound **12** (186 mg, 0.32 mmol), isolated by l.c. from the reaction mixture, was hydrogenated (0.1 MPa) in the presence of 10% Pd–C (80 mg) in methanol (10 mL) and acetic acid (2 mL) for 10 h at room temperature. After the catalyst and the solvent had been removed, acetic anhydride (10 mL) and pyridine (10 mL) were added. The mixture was stirred for 24 h at room temperature and then poured into ice–water (50 mL) and the product extracted with chloroform. The organic layer was washed with saturated $NaHCO_3$ several times, dried (Na_2SO_4), and the solvent removed. The residue was purified by t.l.c. (silica gel) to give **15** (78 mg, 0.20 mmol, 63%), t.l.c. (1:1 hexane.ether) R_F 0.30; ν_{max}^{KBr} 2960 (m), 1740 (s), 1380 (m), 1360 (m), 1230 (s), 1090 (m), and 1035 cm^{-1} (s); ^{1}H-n.m.r. (200 MHz, $CDCl_3$): δ 5.30 (dd, $J_{2,3}$ 9.1, $J_{3,4}$ 9.0 Hz, H-3), 5.07 (dd, $J_{2,3}$ 9.1, $J_{1,2}$ 5.8 Hz, H-2), 4.98 (dd, $J_{3,4} = J_{4,5}$ 9.0 Hz, H-4), 4.34–4.18 (m, H-1), 4.24 (dd, $J_{5,6}$ 5.0, $J_{6a,6b}$ 12.0 Hz, H-6a), 4.05 (dd, $J_{5,6b}$ 2.6, $J_{6a,6b}$ 12.0 Hz, H-6b), 3.88 (ddd, $J_{4,5}$ 9.0, $J_{5,6a}$ 5.0, $J_{5,6b}$ 2.6 Hz, H-5), 2.06 (s, 3 H), 2.02 (s, 3 H), 2.01 (s, 3 H), 2.00 (s, 3 H), 1.86–1.58 (m, 2 H),

1.28–1.10 (m, 1 H), 0.94 (d, 3 H, *J* 7.0 Hz), and 0.88 (d, 3 H, *J* 7.0 Hz).

Anal. Calc. for $C_{18}H_{28}O_9$: C, 55.66; H, 7.26. Found: C, 55.45; H, 7.20.

*2-Methyl-1-(2,3,4,6-tetra-*O*-acetyl-α-*D*-glucopyranosyl)propane*[3] (**16**). — This compound was pepared from 2-bromo-3-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)propene (**14**) (93 mg, 0.144 mmol) by a procedure similar to that described for the preparation of **15** (28 mg, 0.075 mmol), t.l.c. (1:1 hexane–ether) R_F 0.20; ^{1}H-n.m.r. (200 MHZ, $CDCl_3$): δ 5.36 (dd, $J_{2,3} = J_{3,4}$ 9.8 Hz, H-3), 5.11 (dd, $J_{1,2}$ 5.8, $J_{2,3}$ 9.8 Hz, H-2), 5.02 (dd, $J_{3,4} = J_{4,5}$ 9.8 Hz, H-4), 4.28 (dd, $J_{5,6a}$ 5.2, $J_{6a,6b}$ 12.0 Hz, H-6a), 4.26–4.16 (m, H-1), 4.10 (dd, $J_{5,6b}$ 3.0, $J_{6a,6b}$ 12.0 Hz, H-6b), 3.85 (ddd, $J_{4,5}$ 9.8, $J_{5,6a}$ 5.2, $J_{5,6b}$ 3.0 Hz, H-5), 2.10 (s, 3 H), 2.06 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H), 1.90–1.85 (m, 1 H), 1.54–1.24 (m, 3 H), and 0.96 (*t, J* 7.0 Hz, 3 H); identical with the compound obtained from **11** by similar procedure.

Anal. Calc. for $C_{17}H_{26}O_9$: C, 54.54; H, 7.00. Found: C, 54.88; H, 7.24.

*1-(2,3,4,6-Tetra-*O*-acetyl-α-*D*-mannopyranosyl)propane*[3] (**20**). — This compound was prepared from **19** by a procedure similar to that described for the preparation of **15** in 71% yield, t.l.c. (1:1 hexane–ether) R_F 0.20; ^{1}H-n.m.r. (200 MHz, $CDCl_3$): δ 5.34–5.18 (m, 3 H), 4.34 (dd, 1 H, *J* 6.0, 12.0 Hz, 1 H), 4.12 (dd, 1 H, *J* 3.0, 12.0 Hz, H-1), 4.04–3.96 (m, 1 H), 3.94–3.80 (m, 1 H), 2.14 (s, 3 H), 2.10 (s, 3 H), 2.06 (s, 3 H), 2.02 (s, 3 H), 1.92–1.70 (m, 1 H), 1.64–1.30 (m, 3 H), and 0.96 (t, 3 H, *J* 7.0 Hz). On the basis of spectroscopic and chromatographic analysis, **20** was identical with the compound obtained[3] from the α-D anomer of **17**.

Competitive reaction of allylsilanes with benzaldehyde dimethylacetal. — A mixture of 2-propenyltrimethylsilane (**5**; 571 mg, 5.0 mmol), 2-methyl-2-propenyltrimethylsilane (**6**; 645 mg, 5.0 mmol), 2-bromo-2-trimethylsilane (**8**; 968 mg, 5.0 mmol), and benzaldehyde dimethylacetal (158 mg, 1.0 mmol) in dichloromethane (5 mL) was placed in a 50-mL flask and the flask cooled to −78°. To this was added, from a syringe, trimethylsilyl triflate (**9**; 20 mg, 0.1 mmol) and the mixture stirred for 8 h at −78°. After the usual workup, 4-methoxy-4-phenyl-1-butene[9] (**23**; 44 mg, 0.27 mmol) and 4-methoxy-2-methyl-4-phenyl-1-butene[9] (**24**; 115 mg, 0.65 mmol) were isolated by t.l.c. in 27 and 65% yield, respectively. No trace of 2-bromo-4-methoxy-4-phenyl-1-butene (**25**) was detected by g.l.c.

Compound **23**. T.l.c. (3:2 hexane–benzene) R_F 0.45; ^{1}H-n.m.r. (60 MHz, CCl_4): δ 7.33 (s, 5 H), 6.07–4.80 (m, 3 H), 4.10 (t, 1 H, *J* 7 Hz), 3.20 (s, 3 H), and 2.63–2.27 (m, 1 H); m.s.: *m/z* 121 (M^+ −41, 100%) and 77 (19%).

Compound **24**. T.l.c. (3:2 hexane–benzene) R_F 0.50; ^{1}H-n.m.r. (60 MHz, CCl_4): δ 7.20 (s, 5 H), 4.83–4.65 (m, 2 H), 4.20 (t, 1 H, *J* 10 Hz), 3.14 (s, 3 H), 2.33 (m, 2 H), and 1.70 (s, 3 H); m.s.: *m/z* 121 (M^+ −55, 25%), 119 (89%), and 117 (100%).

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ENANTIOSELECTIVE SYNTHESIS OF NEW ANALOGS OF NEPLANOCIN A AND THEIR BIOLOGICAL ACTIVITY

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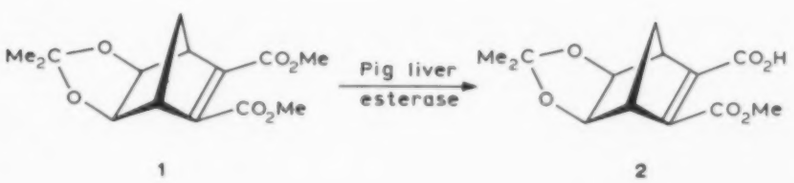
ABSTRACT

Various carbocyclic nucleosides analogs of neplanocin A (such as 5-aminoimidazole-4-carboxamide riboside, uridine, 5-iodouridine, 4-thiouridine, cytidine, thymidine, 2′-deoxyguanosine, ribofuranosylthymine, a 2,2′-anhydroderivative, 2′-deoxycytidine, 2′-deoxythiouridine, and D-arabinofuranosylcytosine analogs) were synthesized from (1*R*, 2*S*, 3*R*)-2,3-isopropylidenedioxy-4-methoxymethyloxymethyl-4-cyclopentenylamine. The cytidine analog was found the most active in inhibiting mouse lymphoma L5178Y cells *in vitro* at a concentration as low as 0.8 μg/mL.



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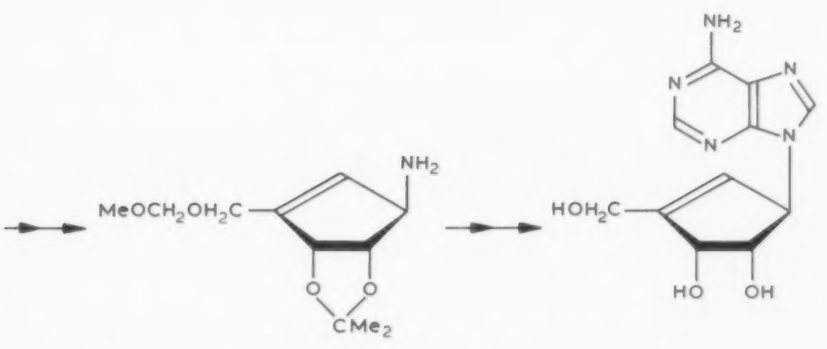

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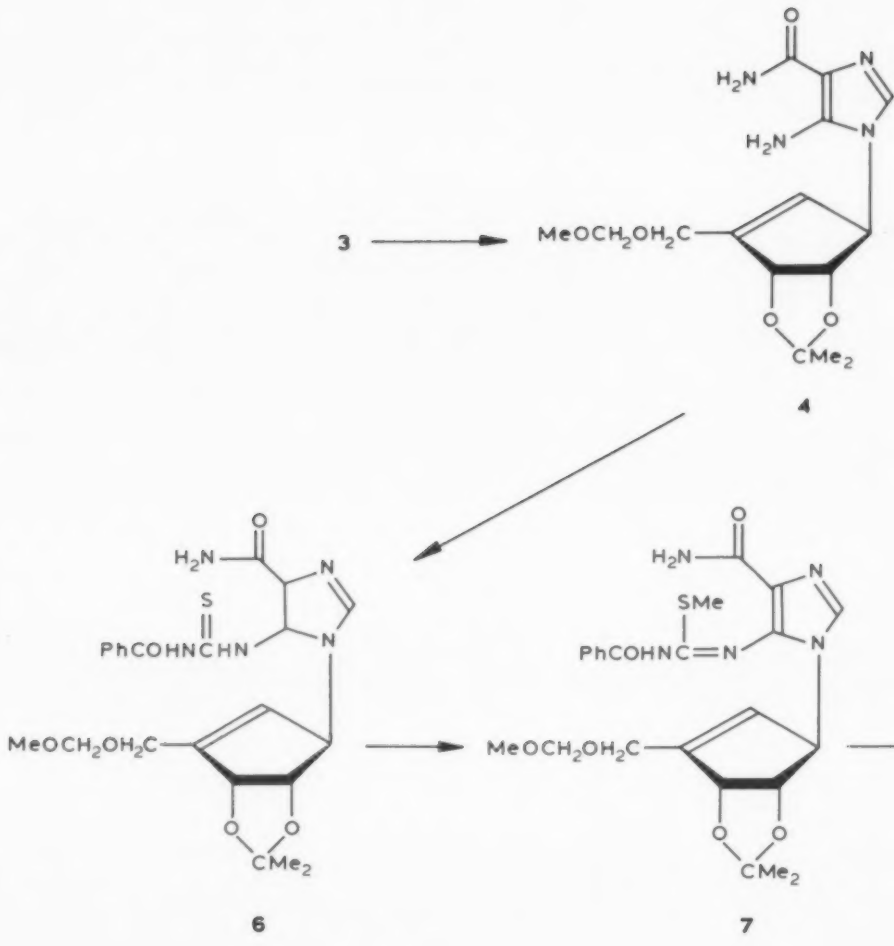
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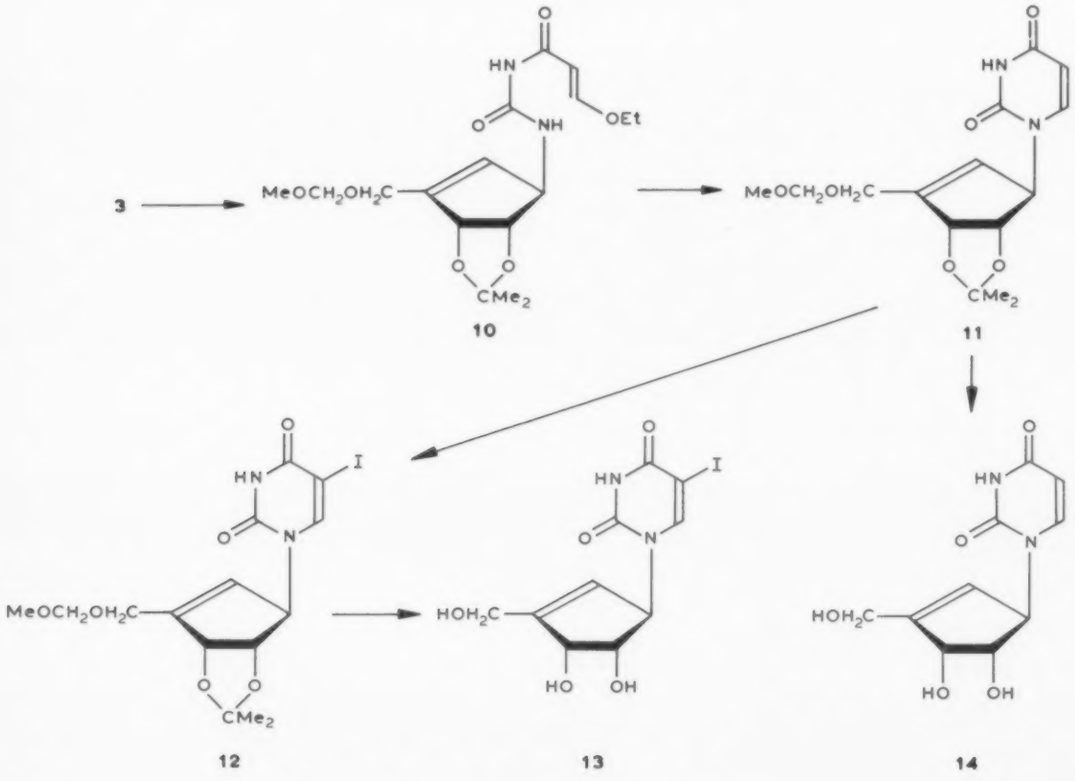
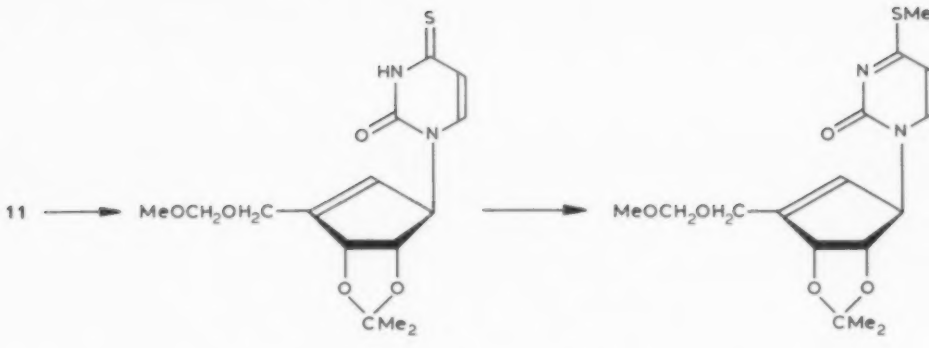
INTRODUCTION

Neplanocin A, isolated from *Actinoplanacea ampullariella sp.* in 1981, is a carbocyclic analog of adenosine having a cyclopentene moiety and exhibits a remarkable antitumor activity against L1210 leukemia in mice[1]. We undertook the selective synthesis of the enantiomer and reported[2] the first and efficient total synthesis of (−)-neplanocin A in 1983 through an optically active half-ester **2**, enzymically generated from a symmetric unsaturated diester **1**. A key intermediate of the synthesis was (1*R*, 2*S*, 3*R*)-2,3-isopropylidenedioxy-4-methoxymethyloxymethyl-4-cyclopentenylamine (**3**), which can be used as a common precursor for the preparation of analogs of neplanocin A. We present herein the enantioselective synthesis of analogs of neplancocin A and their biological activity.

RESULTS AND DISCUSSION

5-Aminoimidazole-4-carboxamide riboside is a key intermediate of the *de novo* biosynthesis of purine nucleosides. Therefore, derivatives of this riboside have been considered as important antimetabolites. Thus, a 5-aminoimidazole-4-carboxamide analog was first synthesized in three steps from **3** according to Shaw and Wilson[3]. The key intermediate **3** was treated with α-amino-α-cyanoacetamide and ethyl orthoformate in acetonitrile to afford the 5-aminoimidazole-4-carboxamide derivative **4** in 72% yield. After deprotection with dilute hydrochloric acid, crude **5** was purified by ion-exchange chromatography to afford pure **5** in 93% yield.

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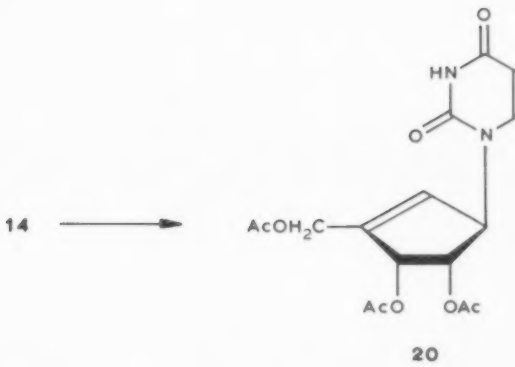
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N
AcO
OAc
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SMe
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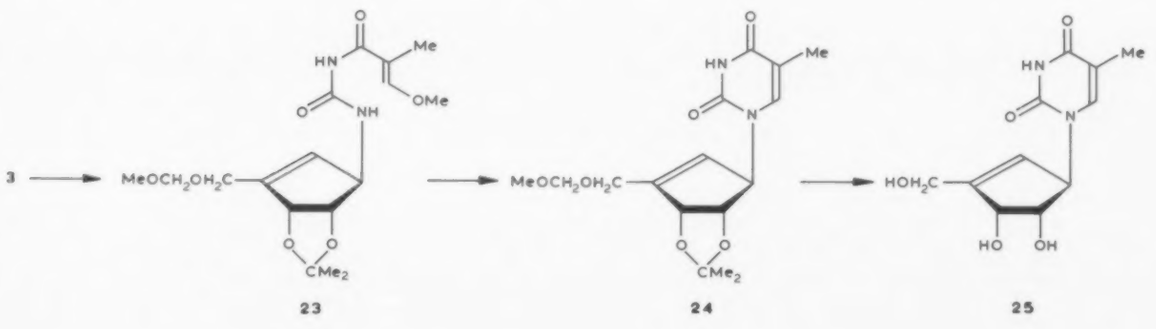
MeOCH2OH2C
CMe2
17
HOH2C
HO
OH
18 R = NH2
19 R = SMe
AcOH2C
AcO
OAc
21
22

The guanosine analog **10** was synthesized in five steps from **3** according to Yamazaki and Okutsu[4]. Treatment of **4** with benzoylisothiocyanate in acetone at room temperature afforded the thiourea derivative **6** in 78% yield. Its methylation proceeded smoothly, to give the methylthio derivative **7** as a colorless oil, after chromatography on silica gel. Treatments with sodium hydroxide gave **9** in 61% yield, and deprotection with hydrochloric acid afforded the guanosine analog **9** in 92% yield.

The uridine analogs were obtained as follows. The cyclopentenylamine **3** was treated with 3-ethoxyacryloylisocyanate[5], generated *in situ* from 3-ethoxyacrolyl chloride and silver isocyanate, to afford the acryloylurea derivative **10** in 91% yield. Cyclization of **10** gave the uridine derivative **11** as a colorless oil in 91% yield. This was deprotected and crude **14** was treated with an ion-exchange resin to afford the pure uridine analog **14** as a colorless syrup in 98% yield. The 5-iodouridine analog **13** was synthesized in four steps from **3** according to Tai-Shun Lin and You-Song Gao[6]. Treatment of **11** with iodine and silver trifluoroacetate afforded **12** in 34% yield, and deprotection, followed by neutralization with an anion-exchange resin, gave **13** in 49% yield.

Various cytidine analogs, such as AraC, cyclo C, and 5-FC, are in clinical use as antitumor agents and a carbocyclic cytidine analog (Carbodine) was found to be active against L1210 leukemia[7]. Therefore, we investigated the biological activity of the cytidine analog of the cyclopentenylnucleoside, neplanocin A. In a first approach to the preparation of the cytidine analog **18**, thiation[8] of the uridine derivative **11** produced the 4-thiouridine derivative **15** in 45% yield with a 50% recovery of **11**. Methylation of **15** in 89% yield, followed by amination of **16** ammonia to give **17** in 91% yield, and finally deprotection with hydrochloric acid afforded the cytidine analog **18** in 94% yield. As the yield of the first step was low, a second approach was investigated. Acetylation of the uridine analog **14** afforded the tri-*O*-acetyl derivative **20** in 91% yield, in addition to the N^3,2′,3′,6′-tetraacetyl derivative in 7% yield. Treatment of **20** with phosphorus pentasulfide afforded the 4-thio derivative **21** in 83% yield, which was methylated to give **19**, further aminated to afford the crystalline cytidine analog **18** in 94% yield. The 4-thiouridine analog **22** was obtained from **21** by treatment with ammonia.

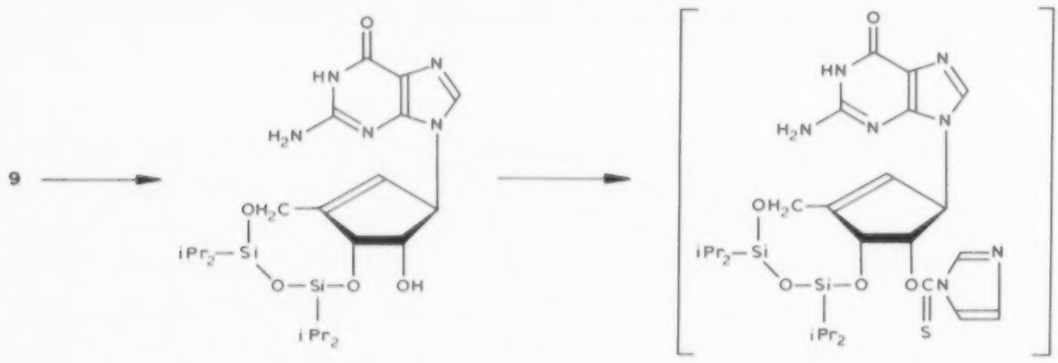
The thymine base was introduced in the same manner as the uracil base. Treatment of the free amine **3** with 3-methoxy-2-methylacryloyl isocyanate[9] afford-

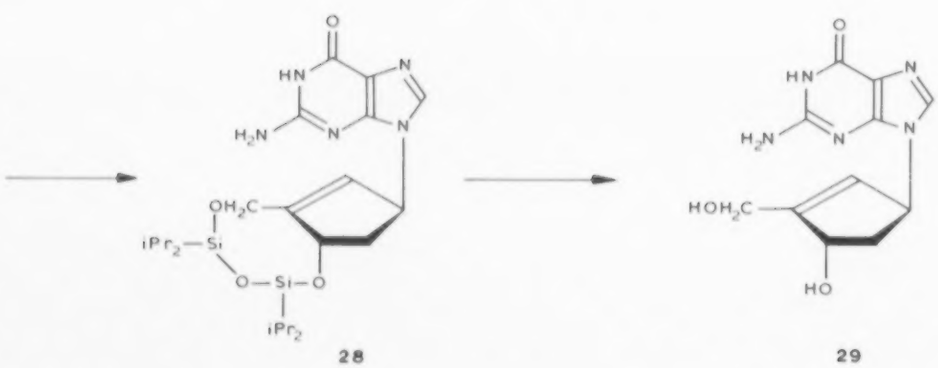


ed the ureido derivative **23** in 87% yield. Cyclization was achieved in acetone with ammonium hydroxide to give, in a fairly good yield, **24** the structure of which was readily established by the u.v. spectrum and other analyses as for the uracil derivative **11**. Hydrolysis of **24** with trifluoroacetic acid gave **25** in crystalline form, in 75% yield after chromatographic purification.

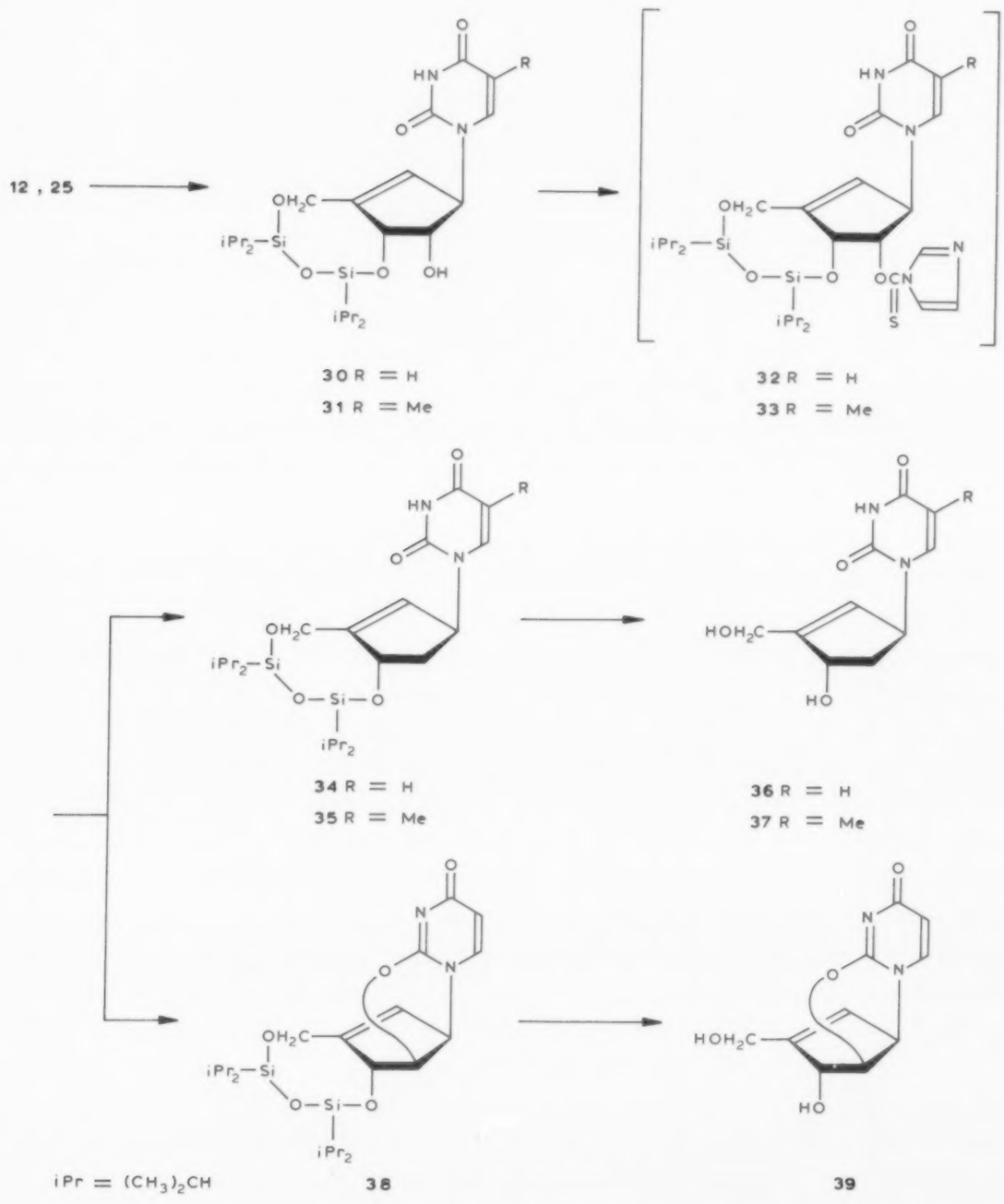
The easy 2′-deoxygenation of ribonucleosides and neplanocin A[10], by a radical reduction of a 2′-deoxy-2′-halogeno or thiocarbonyl derivative with tributyltin hydride in the presence of azo(isobutyronitrile) (Barton reaction), was also applied successfully in the present work. First, OH-3- and -6 of **9** of the cyclopentene moiety were protected by the Markiewicz reagent[10,11], 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane, in the presence of imidazole to give **20** in 58% yield. Deoxygenation of **20** was performed without isolation of the intermediate **27** by treatment with *N,N*-thiocarbonyldiimidazole, followed by reduction with tributyltin hydride, in the presence of a catalytic amount of azo(isobutyronitrile), to give **28** in 40% yield from **26**. The ^{1}H-n.m.r. spectrum of **28** exhibited a characteristic signal for H-2′ at δ 2.32 as a multiplet. Deprotection with tetrabutylammonium fluoride in THF afforded the desired compound **29** in 85% yield.

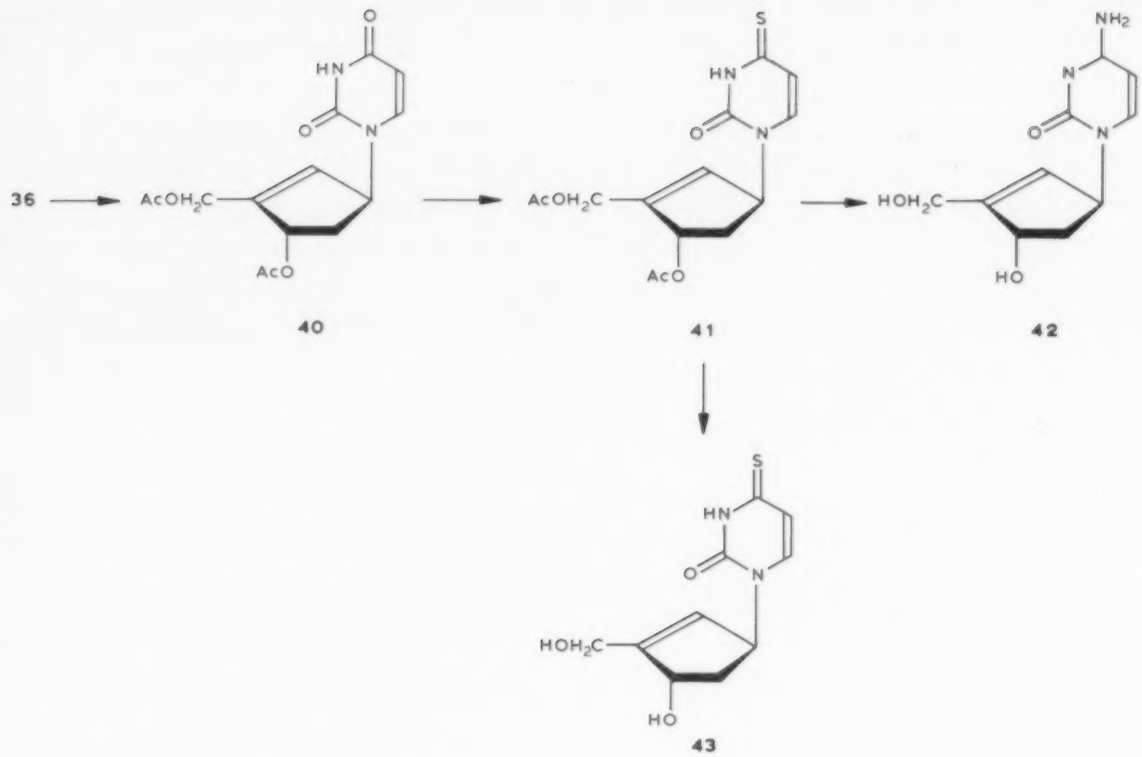
The deoxygenation reported in our previous study[10] was also applied to the uracil (**12**) and thymine (**25**) analogs. They were protected in the usual manner to give **30** (71%) and **31** (68%), respectively. Attempts to deoxygenate **30** in acetonitrile through *O*-thiocarbonylation, followed by homolytic cleavage, gave **34** (45%) to-





gether with the 2,2′-anhydro derivative **38** (30%), which were readily separated by silica gel column chromatography. In the ^{1}H-n.m.r. spectrum, **34** showed signals for H-2′a (ddd) and H-2′b (ddd) at δ 2.06 and 2.44, respectively. The structure was further confirmed by mass spectrometry (*m/z* 466, M^+) and other analyses. The ^{1}H-n.m.r. spectrum of **38** exhibited a signal for H-2′ at δ 5.21–5.41 (m), overlapped by the signals for H-1′ and H-3′, as well as a parent peak in the f.a.b. mass spectrum at *m/z* 465 (MH^+). The ratio of **38** to **34** seemed to increase with higher temperatures. The 2,2′-anhydro derivative **38** was used for the synthesis of the *arabino*-pyrimidine nucleoside **49**. Treatment of **30** with *N,N′*-thiocarbonyldiimidazole, followed by homolytic cleavage of **32** with tributyltin hydride furnished **34** (76%)





exclusively. Similarly, **35** was obtained from **31** in 77% yield; its ^{1}H-n.m.r. spectrum showed the characteristic signals of H-2′a(m) and H-2′b(m) at δ 2.12 and 2.35, respectively. Both **34** and **35** were deprotected with tetrabutylammonium fluoride to afford crystalline **36** and **37** in 71 and 92% yield, respectively, and similarly **38** furnished **39** in a quantitative yield.

The di-*O*-acetyl derivative **40** of the 2′-deoxyuridine derivative **36** was thiated with phosphorus pentasulfide to give **41** in 87% yield, and successive methylation and ammonolysis afforded the 2′-deoxycytidine analog **42**. The 2′-deoxy-4-thiouridine analog **43** was obtained from **41** by treatment with ammonia.

In general, D-arabinosylnucleosides are recognized as deoxynucleosides by the cell system[13], but it is noteworthy that the cytidine analog **18** possesses a marked activity against L-1210 and B-16 melanoma system *in vivo* (Table I). Therefore, we synthesized the analog **48** having the D-arabino configuration in order to compare its activity with that of AraC and the cytidine analog **18**. Among the many methods of synthesis of arabinosylpyrimidine nucleosides[14], that using the hydrolytic cleavage of the 2,2′-anhydro derivative **39** seemed the most suitable. Treatment of 3′,5′-*O*-silyl protected uridine compounds with trifluoromethanesulfonyl chloride furnished the 2,2′-*O*-anhydrouridine exclusively[12]. This reaction may proceed by the intramolecular SN2 attack of the oxygen atom of the uridine base to the 2′-position (2′-OTf group) of the sugar residue. Therefore, **30** was treated with trifluoromethanesulfonyl chloride in the presence of *N,N*-dimethylaminopyridine to give, in 53% yield, **38** which was identical in all respects with the compound obtained as a

TABLE I

EFFECT OF NEPLANOCIN A AND CYTIDINE ANALOG (**18**) ON THE LIFE SPAN OF MICE BEARING L1210 LEUKEMIA AND B16 MELANOMA[a]

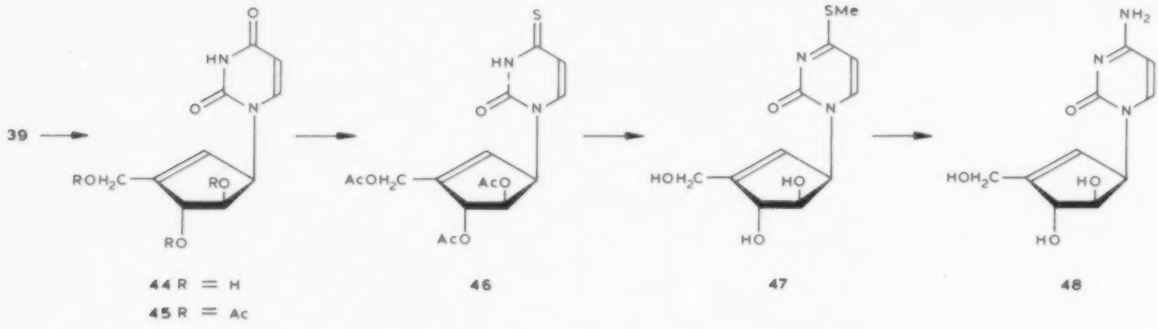
Compound	*L1210 Leukemia*		*B16 Melanoma*	
	Dose (mg/kg/day)	T/C *(%)*	*Dose (mg/kg/day)*	T/C *(%)*
Neplanocin A	0.25	140		
	0.5	147	0.5	106
	1.0	138	1.0	106
	2.5	159	2.5	114
	5.0	Toxic		
Cytidine analog **18**	0.1	108	0.1	119
	0.25	131	0.25	128
	0.5	149	0.5	133
	1.0	177	1.0	144
	2.5	Toxic		
Ara-C	50	185	50	122
	100	193	100	125
	250	207	250	119
	500	218	500	Toxic
	1000	Toxic		
5-Fu	5	219		
	10	220	10	119
	25	225	25	125
	50	146	50	Toxic
	100	Toxic		

[a] Groups of 6 female CD_2F_1 mice or male $B_6D_2F_2$ mice received intraperitoneal implants of L1210 leukemia cells (10^5/mouse), or B16 melanoma homogenates (0.5 mL/mouse), respectively, on day 0, according to the protocols described by Geran *et al.*[17]. Compounds were given intraperitoneally on days 1–5. The results are expressed as *T/C* values calculated from median survival times, where *T* and *C* are values of treated and untreated groups, respectively.

by-product in the radical reduction of **32**. After deprotection of **38** in the usual manner, alkaline hydrolysis of **39** gave **44** which was acetylated without purification to exclusively furnish the triacetate **45** as a syrup in 98% yield; no N^3,2′,3′,6′-tetra-acetyl by-product was observed in this case. Thiation of **45** gave **46** in 90% yield, and methylation, followed by treatment with a large excess of saturated methanolic ammonia, afforded crystalline **48** in 43% yield from **46**; its structure was assertained by ^{1}H-n.m.r. spectroscopy and mass spectrometry.

Biological activity. — Compounds, **5, 9, 13, 14, 18, 22, 25, 29, 36, 30, 39, 42, 43,** and **48** were evaluated for growth-inhibitory activity of mouse lymphoma L5178Y cells *in vitro*. As shown in Table II, the cytidine analog **18** and neplanocin A inhibited the growth at a concentration as low as 0.8 μg/mL, whereas the other 13 analogs had no effect, even at the highest concentration tested, 100 μg/mL. Recent-

ly, **18** was synthesized also from D-ribono-1,4-lactone by Marquez and assoc.[15] and shown to exhibit potent cytotoxicity. It seems worthwhile to note that **18** acts as inhibitors of uridine kinase[15] and CTP synthesis[16]. The antitumor activities of **18** and neplanocin A, compounds having potent cytotoxicity for L5178Y cells cultures, were tested against mouse leukemia L1210 and mouse melanoma B16. In the present study, the compounds were given intraperitoneally to mice, inoculated intraperitoneally with tumors; the results are shown in Table I. The cytidine analog **18**



and neplanocin A increased the life span of the leukemic mice by 77% at a dose of 1 mg/kg/day and 59% at 2.5 mg/kg/day, respectively, over the controls. Ara-C and 5-FU, used as reference antitumor drugs, were more effective in increasing the life span of leukemic mice than **18** and neplanocin A. Against mouse melanoma B16, **18** was found to be the most active among the tested compounds; it increased the life

TABLE II

INHIBITION OF GROWTH OF CULTURED L5178Y CELLS BY NEPLANOCIN A ANALOGS[a]

Compound	*Cytotoxic concentration (μg/mL)*
5	>100
9	>100
14	>100
13	>100
18	0.8
22	>100
25	>100
29	>100
36	>100
37	>100
39	>100
42	>100
43	>100
48	>100
Neplanocin A	0.8

[a] L5178Y cells were suspended in Fischer's medium supplemented with 10% fetal bovine serum at cell concentrations ranging from 5 to 10 × 10^4 cells/mL. Cell growth was checked 24 h after incubating at 37° in a humidified incubator passing 5% CO_2–95% air with or without test compounds.

span of tumor-bearing mice by 44% over the control at a dose of 1 mg/kg/day. The other three compounds tested were found to be inactive (ILS, increase in the life span over control, $\geqq$125%). On the basis of these findings, a further evaluation study on the antitumor activity of the cytidine analog **18** in a variety of tumors is now under progress.

EXPERIMENTAL

General methods. — Melting points were determined with Yanagimoto (MP-3) and Yamato (MP-21) micromelting point apparatus and are uncorrected. Optical rotations were measured with a Horiba SEPA-200 or JASCO DIP-360 polarimeter. U.v. spectra were recorded with a Shimadzu UV-250 or Hitachi 320 spectrophotometer. I.r. spectra were recorded with a Hitachi 260-50, JASCO IR-810, or Shimadzu IR-435 spectrophotometer. ^{1}H-N.m.r. spectra were recorded for solutions in (2H)chloroform of di($^2H_3$)methyl sulfoxide with tetramethylsilane and sodium 4,4-dimethyl-4-silapentane-1-sulfonate (DDS) as an internal standard, with a JEOL FX-100-FT, JNM-PS-100, or Hitachi R-90 spectrometer. All exchangeable protons were confirmed by addition of D_2O. Mass spectra (m.s.) were measured on JEOL JMS D-300 (CI, FAB or EI) or JMS-01SG spectrometers. T.l.c. was carried out on Merck pre-coated silica gel $60F_{254}$ plates, and silica gel column chromatography was performed on Wako-gel C-200, Merck Kieselgel 60 Art 7734 or 9385.

*5 - Amino - 1[(1*R*, 2*S*, 3*R*) - 2,3 - isopropylidenedioxy - 4 - methoxymethyloxy - methyl-4-cyclopenten-l-yl]imidazole-4-carboxamide* (**4**). — To a solution of α-amino-α-cyanoacetamide (1.0 g, 0.01 mol) in dry acetonitrile (40 mL) was added triethyl orthoformate (1.64 g, 0.011 mol), and the mixture was refluxed with stirring for 30 min under an Ar atmosphere. A solution of **3** (1.10 g) and triethylamine (0.60 mL) in dry acetonitrile (25 mL) was added dropwise to the cooled mixture, which was refluxed with stirring for 3 h. The solvent was removed under reduced pressure, and the residue purified by silica gel column chromatography (20:1 chloroform–methanol) to give **4** (1.16 g, 72% yield), yellow crystals, m.p. 141.5–143°; $[\alpha]_D^{20}$ −34.2° (*c* 0.96, chloroform); R_F 0.67 (3:1:1 ethyl acetate–ethanol–water 0.67; ν_{max}^{KBr} 3425, 3330, 3175, 1650, 1615, 1547, 1468, and 1385 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$–Me_4Si): δ 1.35 and 1.47 [2 s, 6 H, $C(CH_3)_2$], 3.41 (s, 3 H, OMe), 4.30 (br.s, 2 H, CH_2O), 4.58 and 5.25 (2 d, 2 H, *J* 5.8 Hz, 2OCH), 4.71 (s, 2 H, OCH_2O), 4.94 (br.s, 1 H, NCH), 5.07 (br.s, 4 H, $CONH_2$, NH_2), 5.82 (br.s, 1 H, –CH=), and 6.86 (s, 1 H, arom.); e.i.m.s.: *m/z* 338 (M^+), 281, and 149.

Anal. Calc. for $C_{15}H_{22}N_4O_5$: C, 53.25; H, 6.55; N, 16.56. Found: C, 52.99; H, 6.52; N, 16.64.

*5-Amino-1-[(1*R*, 2*S*, 3*R*)-2,3-dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]imidazole-4-carboxamide* (**5**). — Compound **4** (244 mg) was dissolved in methanol (20 mL) and 2M HCl (20 mL), and the solution stirred at 30–35° for 1 day. Methanol was removed under reduced pressure, and the residual solution passed through Amberlite CG-120 (H^+) cation-exchange resin. Elution with 0.07M NH_4OH

subsequent to washing with water and evaporation of the eluent under reduced pressure gave **5** (170 mg, 93% yield), pale-yellow crystals, m.p. > 220° (dec.); $[\alpha]_D^{20}$ −87.1° (*c* 0.16, dimethyl sulfoxide; R_F (3:1:1 ethyl acetate–ethanol–water) 0.46; ν_{max}^{KBr} 3450, 3350, 3250, 1655, 1635, 1550, and 1455 cm^{-1}; ^{1}H-n.m.r. [$(CD_3)_2SO$–$CDCl_3$; Me_4Si)]: δ 3.91 (t, 1 H, *J* 5.5 Hz, OCH), 4.12 (br.s, 2 H, CH_2OH), 4.35 (d, 1 H, *J* 5.5 Hz, OCH), 4.90 (br.s, 1 H, NCH), 5.74 (br.s, 1 H, –CH=), 5.64 and 6.68 (br, 4 H, $CONH_2$, NH_2), and 7.02 (s, 1 H, arom.); e.i.m.s.: *m/z* 222, 220 (M^+ − 2OH) 207, and 205.

Anal. Calc. for $C_{10}H_{14}N_4O_4 \cdot 0.5\ H_2O$: C, 45.63; H, 5.74; N, 21.28. Found: C, 45.76; H, 5.37; N, 20.83.

5-(N-Benzoylthiocarbamoyl)amino-1-[(1R,2S,3R)-2,3-isopropylidenedioxy-4-methoxymethyloxymethyl-4-cyclopenten-1-yl]imidazole-4-carboxamide (**6**). — To a solution of **4** (50 mg) in dry acetone (3 mL) was added dropwise benzoyl isothiocyanate (150 mg) in dry acetone (4 mL). The mixture was stirred at room temperature for 4 h, poured into saturated aqueous $NaHCO_3$ and extracted with dichloromethane several times. The organic layer was washed with water until neutral, and evaporated under reduced pressure, after being dried by passing through a phase-separating paper (Whatman 1PS), to afford a crude syrup. This was purified by silica gel column chromatography with stepwise elution with dichloromethane–methanol 50:1 to 30:1 to 20:1) to give **6** (70 mg, 95% yield) foam, R_F (9:1 dichloromethane–methanol) 0.53; ν_{max}^{film} 3500, 3350, 3200, 1670, 1605, 1490, and 1380 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$; Me_4Si): δ 1.32 and 1.40 [2 s, 6 H, $C(CH_3)_2$], 3.38 (s, 3 H, OMe), 4.27 (br.s, 2 H, CH_2O) 4.65 (s, 2 H, OCH_2O), 4.70 and 5.26 (d, 2 H, *J* unknown, 2 OCH), 5.24 (br. s, 1 H, NCH), 5.68 (br.s, 1 H, –CSN*H*–), 5.86 (br. s, 1 H, –CH=), 6.95 (br, 2 H, $CONH_2$), 7.29 (s, 1 H, imidazole proton), 7.52 and 7.88 (m, 5 H, PhCO), and 9.56 (br.s, 1 H, CSN*H*CO); e.i.m.s.: *m/z* 501 (M^+) and 486 (M^+ − Me).

5-(N-Benzoyl-S-methylisothiocarbamoyl)amino-1-[(1R, 2S, 3R)-2,3-isopropylidenedioxy-4-methoxymethyloxymethyl-4-cyclopenten-1-yl]imidazole-4-carboxamide (**7**). — To a solution of **6** (50 mg) and iodemethane (60 μL) in methanol (5 mL) was added M NaOH (0.2 mL) dropwise under stirring at room temperature. The mixture was stirred for 1 h at ambient temperature, the reaction quenched by addition of acetic acid to neutrality, and the solvent removed under reduced pressure. The residue was extracted with ethyl acetate several times and the extract washed with water. The organic layer was passed through Whatman 1PS filter paper and evaporated under reduced pressure. The residue was purified by silica gel column chromatography with ethyl acetate as an eluent to give **7** (43 mg, 84% yield) as a colorless syrup by evaporation of the eluate under reduced pressure, R_F (9:1 dichloromethane–methanol) 0.66; ν_{max}^{film} 3460, 3350, 1650, 1610, 1575, and 1370 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$; Me_4Si) 1.32 and 1.41 [2 s, 6 H, $C(CH_3)_2$], 2.60 (s, 3 H, SMe), 3.39 (s, 3 H, OMe), 4.29 (br.s, 2 H, CH_2O), 4.59 and 5.16 (2 d, *J* 6 Hz, 2 H, 2 OCH), 4.68 (s, 2 H, OCH_2O), 5.24 (br.s, 1 H, NCH), 5.72 (br.s, 1 H, –CH=), 5.84 (br.s, 1 H, CONH–), 7.11 (s, 1 H, imidazole H), 7.34 and 7.83 (m, 5 H, PhCO); e.i.m.s.:

m/z 515 (M^+), 468 (M^+ − SMe), 467, 320, and 262.

9-[(1R, 2S, 3R)-2,3-Isopropylidenedioxy-4-methoxymethyloxymethyl-4-cyclopenten-1-yl]guanine (**8**). — To a solution of **7** (75 mg) in methanol (4 mL) was added 6M NaOH (4 mL), and the mixture stirred for 4 h at 100–110°. After the mixture had been cooled in an ice bath, rapid crystallization occurred on neutralization with dilute HCl. Methanol was removed under reduced pressure, and filtration gave **8** (37 mg, 70% yield), colorless crystals, m.p. >270° (dec.), R_F (3:1:1 ethylacetate–ethanol–water) 0.60; λ_{max}^{MeOH} 256.5 and 232 nm; ν_{max}^{KBr} 3400, 3200, 1700, 1640, 1605, 1540, and 1380 cm^{-1}; ^{1}H-n.m.r. [$(CD_3)_2SO$–$CDCl_3$; MeSi]: δ 1.29 and 1.37 [2 s, 6 H, $C(CH_3)_2$], 3.31 (s, 3 H, OMe), 4.20 (s, 2 H, CH_2O), 4.59 and 5.38 (2 d, *J* 5.5 Hz, 2 H, 2 OCH), 4.64 (s, 2 H, OCH_2O) 5.26 (br.s, 1 H, NCH), 5.70 (s, 1 H, –CH=), 6.48 (br.s, 1 H, CONH), and 7.44 (s, 1 H, arom.); e.i.m.s.: *m/z* 363 (M^+), 348 (M^+ − Me), 311, 284, 152 (G + 2), and 151 (G + 1).

9-[(1R, 2S, 3R)-2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]guanine (**9**). — Compound **8** (33 mg) was dissolved in methanol (1 mL) and 2M HCl (1 mL), and the mixture was stirred for 2 days at room temperature. Methanol was removed by evaporation under reduced pressure and the residual solution was applied to a column of Dowex 50 (H^+) cation-exchange resin. Elution with 0.1M NH_4OH, subsequent to washing with water, followed by evaporation under reduced pressure afforded **9** (20 mg, 81% yield), colorless needles after crystallization from water, m.p. >220° (dec.), $[\alpha]_D^{20}$ −87° (*c* 0.15, *N,N*-dimethylformamide); R_F (3:1:1 ethyl acetate–ethanol–water) 0.26; $\lambda_{max}^{H_2O}$ 254.5, $\lambda_{min}^{H_2O}$ 229.5nm; ν_{max}^{KBr} 3400, 3200, 1740, 1692, 1640, 1613, and 1540 cm^{-1}; ^{1}H-n.m.r. [$(CD_3)_2SO$–$CDCl_3$; Me_4Si]: δ 3.32 (br, 2 H, 2 OH), 4.10 (s, 2 H, CH_2OH), 4.16 and 4.23 (t, 1 H, *J* 5.3 Hz; d, 1 H, *J* 5.3 Hz; 2 OCH), 5.14 (br.s, 1 H, NCH), 5.64 (d, 1 H, *J* 1.8 Hz, –CH=), 6.60 (br.s, 1 H, CONH), and 7.55 (s, 1 H, arom.); e.i.m.s.: *m/z* 279 (M^+), 207, 183, 165, and 152 (G + 2).

(1R, 2S, 3R)-1-[N-(3-Ethoxyacryloyl)ureido]-2,3-isopropylidenedioxy-4-methoxymethyloxymethyl-4-cyclopentene (**10**). — Compound **3** (544 mg) was dissolved in dry *N,N*-dimethylformamide (20 mL) and the solution cooled to −30 to −45° in a dry ice–acetone bath. To this mixture was added a solution of 3-ethoxy-2-propenoyl isocyanate [prepared from 3-ethoxy-2-propenoyl chloride (650 mg) and AgNCO (1.44 g) by heating in dry benzene] dropwise under an Ar atmosphere. The mixture was stirred for 1 h each at −30° and at room temperature, and then poured into ice-cooled, satd. $NaHCO_3$ with vigorous stirring and extracted with ethyl acetate three times. The combined organic layer was washed with water, dried by passing through Whatman 1PS, and evaporated under reduced pressure. The residue was chromatographed in a column of silica gel with 1:2 ethyl acetate–hexane to give **10** (800 mg, 91% yield), colorless syrup, R_F (1:1 ethyl acetate–hexane) 0.27; ν_{max}^{film} 3250, 3100, 1700, 1675, 1615, 1535, and 1380 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$; Me_4Si): δ 1.32 and 1.39 [2 s, 6 H, $C(CH_3)_2$], 1.35 (t, 3 H, *J* 6.8 Hz, CH_2CH_3), 3.38 (s, 3 H, OMe), 3.97 (q, 2 H, *J* 6.8 Hz, OCH_2CH_3), 4.19 (s, 2 H, CH_2O), 4.55 and 4.79 (d, 1 H, *J* 6 Hz; m, 1 H, 2 OCH), 4.67 (s, 2 H, OCH_2O), 5.14 (br.d, 1H, *J* 5.5 Hz, NCH),

5.38 (d, 1 H, *J* 12.5 Hz, -COCH=), 5.66 (s, 1 H, -CH=), 7.61 (d, 1 H, *J* 12.5 Hz, =C*H*-OEt), 8.63 (d, 1 H, *J* 7 Hz, CHN*H*CO), and 9.26 (s, 1 H, CONHCO); e.i.m.s.: *m/z* 355 (M^+ − Me), 309, 281, 267, 257, and 252.

*1-[(1*R*, 2*S*, 3*R*)-2,3-Isopropylidenedioxy-4-methoxymethyloxymethyl-4-cyclopenten-1-yl]-2,4-(1*H*, 3*H*)-pyrimidinedione* (**11**). — To a solution of **10** (404 mg) in acetone (10 mL) was added 2.8% NH_4OH, (30 mL), and the mixture stirred with reflux for 10 h. After being cooled to ambient temperature, the mixture was evaporated under reduced pressure. The residue was chromatographed in a column of silica gel with 1:2 ethyl acetate–hexane to give **11** (321 mg, 91% yield), colorless foam, $[\alpha]_D^{20}$ −53.5° (*c* 0.66, chloroform), R_F (ethyl acetate) 0.34; ν_{max}^{film} 3200, 1680, 1450, 1370, and 1230 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$; Me_4Si): δ 1.35 and 1.44 [2 s, 6 H, $C(CH_3)_2$], 3.40 (s, 3 H, OMe), 4.28 (br.s, 2 H, CH_2O), 4.59 and 5.23 (2 d, 2 H, *J* 5.8 Hz, 2 OCH), 4.70 (s, 2 H, OCH_2O), 5.38 (br.s, 1 H, NCH), 5.59 (br.s, 1 H, -CH=), 5.68 (dd, 1 H, *J* 1.5, 8 Hz, COCH=), 7.05 (d, 1 H, *J* 8 Hz, NCH=), and 9.67 (br.s, 1 H, CONHCO); e.i.m.s.: *m/z* 309 (M^+ − Me), 267, 263, and 235.

*1-[(1*R*, 2*S*, 3*R*)-2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-2,4(1*H*, 3*H*)-pyrimidinedione* (**14**). — (*a*). A solution of **11** (3.0 g) in trifluoroacetic acid (30 mL) and water (30 mL) was stirred for 2 days at room temperature. The mixture was evaporated and the residue coevaporated to dryness with ethanol several times under reduced pressure. It was purified by silica gel column chromatography with 4:1 chloroform–methanol as an eluent to give **14** (1.71 g, 77% yield), colorless foam, $[\alpha]_D^{20}$ −84° (*c* 1.19, methanol), R_F (3:1:1 ethyl acetate–ethanol–water) 0.41; λ_{max}^{MeOH} 270 nm; ν_{max}^{film} 3350, 1675, 1460, 1388, and 1255 cm^{-1}; ^{1}H-n.m.r. (CD_3OD–$CDCl_3$; Me_4Si): δ 4.04 (t, 1 H, *J* 5.5 Hz, OCH), 4.27 (br.s, 2 H, CH_2OH), 4.52 (d, 1 H, *J* 5.5 Hz, OCH), 5.48 (br.s, 1 H, NCH), 5.69 (d, 1 H, *J* 2 Hz, -CH=), 5.70 (d, 1 H, *J* 8 Hz, -COCH=), and 7.38 (d, 1 H, *J* 8 Hz, -NCH=); e.i.m.s.: *m/z* 223 (M^+ − OH), 207 (M^+ − 2 OH), 167, 161, 112 (U + 1), and 110 (U − 1).

(*b*). A mixture of **11** (47 mg) in methanol (4 mL) and 2M HCl (4 mL) was stirred for 1 day at 30–35°. Methanol was removed under reduced pressure, and the residual solution made neutral with Diaion WA30 (OH^-) ion-exchange resin. After filtration, the solution was concentrated to dryness under reduced pressure to furnish **14** (34 mg, 98% yield) as a colorless foam.

*5-Iodo-1-[(1*R*, 2*S*, 3*R*)-2,3-isopropylidenedioxy-4-methoxymethyloxymethyl-4-cyclopenten-1-yl]-2,4-(1*H*, 3*H*)-pyrimidinedione* (**12**). — To a solution of **11** (2.00 g) in dry dichloromethane (120 mL) was added silver trifluoroacetate (2.70 g), and a solution of I_2 (2.30 g) in dichloromethane (15 mL) was added dropwise under cooling in an ice bath under an N_2 atmosphere. After being stirred for 1 h at the same temperature, the mixture was poured into ice-cold, satd. $NaHCO_3$, and the insoluble material was filtered off with Celite. The filtrate was partitioned with ethyl acetate several times, and the combined organic layer dried by passing through Whatman 1PS and evaporated to dryness under reduced pressure. The residue was purified by chromatography in a silica gel column with 1:1 ethyl acetate–hexane, to give **12** (1.00 g, 34% yield), m.p. 195–196°, $[\alpha]_D^{23}$ −87.5° (*c* 0.3, chloroform); R_F (1:1

ethyl acetate–hexane) 0.26; λ_{max}^{MeOH} 290, λ_{min}^{MeOH} 247 nm; ν_{max}^{KBr} 3160, 3040, 1695, 1690, 1608, 1440, 1090, and 1040 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$; Me_4Si): δ 1.35 and 1.44 [2 s, 6 H, $C(CH_3)_2$], 3.40 (s, 3 H, OMe), 4.29 (br.s, 2 H, $-CH_2O$), 4.57 and 5.23 (2 d, 2 H, *J* 6 Hz, 2 OCH), 4.70 (s, 2 H, OCH_2O), 5.36 (br.s, 1 H, NCH), 5.58 (br.s, 1 H, –CH=), 7.41 (s, 1 H, N–CH=), and 8.78 (br.s, 1 H, CONHCO); e.i.m.s.: *m/z* 450 (M^+), 435 (M^+ – Me), 331, 283, 156, 155, and 123.

Anal. Calc. for $C_{15}H_{19}IN_2O_6$: C, 40.02; H, 4.25; N, 6.22. Found: C, 39.83; H, 4.23; N, 6.21.

*1-[(1*R*, 2*S*, 3*R*)-2,3-Dihydroxy-4-hydromethyl-4-cyclopenten-l-yl]-5-iodo-2,4-(1*H*, 3*H*)-pyrimidinedione* (**13**). — Compound **12** (1.0 g) was dissolved in methanol (10 mL) and 3M HCl (10 mL), and the mixture stirred for 24 h at ambient temperature. Methanol was removed by evaporation under reduced pressure, and the residual solution was applied onto a column of Diaion WA30 (OH^-) ion-exchange resin. Elution with water, followed by evaporation under reduced pressure gave **13** (425 mg, 52% yield) which was crystallized from 4:1 ethanol–methanol, needles, m.p. 123–124°, $[\alpha]_D^{23}$ −114° (*c* 0.195, methanol, R_F (3:1:1 ethyl acetate–ethanol–water) 0.64; λ_{max}^{MeOH} 292, λ_{min}^{MeOH} 246.5nm; ν_{max}^{KBr} 3380, 1680, 1610, 1425, 1260, and 1118 cm^{-1}; ^{1}H-n.m.r. [$(CD_3)_2SO$; Me_4Si]: δ 3.92 (t, 1 H, *J* 5.5 Hz, OCH), 4.08 (br.s, 2 H, CH_2OH), 4.33 (d, 1 H, *J* 5.5 Hz, OCH), 4.88 (br, 3 H, 3 OH), 5.30 (br.s, 1 H, NCH), 5.53 (br.s, 1 H, –CH=), 7.70 (s, 1 H, N–CH=), and 11.52 (br, 1 H, CONHCO); 366 (M^+), 348 ($M^+ - H_2O$), 330 ($M^+ - 2\ H_2O$), 287, 276, 254, and 238 (5 – IU + 1).

Anal. Calc. for $C_{10}H_{11}IN_2O_5 \cdot EtOH$: C, 34.97; H, 4.16; N, 6.80. Found: C, 34.63; H, 4.12; N, 6.77.

*1-[(1*R*, 2*S*, 3*R*)-2,3-Isopropylidenedioxy-4-methoxymethyloxymethyl-4-cyclopenten-1-yl]-2-oxo-4-thioxo-(1*H*, 3*H*)-pyrimidine* (**15**). — To a solution of compound **11** (40 mg) in dry pyridine (1 mL) was added P_2S_5 (67 mg), and the mixture stirred for 2 h at 95–100°. After being cooled to room temperature, the mixture was evaporated under reduced pressure and the residue extracted several times with dichloromethane. The combined organic layer was washed with water and evaporated to dryness under reduced pressure. The residue was applied onto a silica gel column which was developed with 1:1 ethyl acetate–hexane to give [along with recovered starting material **11** (20 mg, 50% yield)] **15** (18 mg, 45% yield), slightly yellow syrup, R_F (ethyl acetate) 0.77; ν_{max}^{film} 1705, 1610, 1450, 1380, and 1235 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$;Me_4Si): δ 1.36 and 1.44 [2 s, 6 H, $C(CH_3)_2$], 3.40 (s, 3 H, OMe), 4.29 (s, 2 H, CH_2O), 4.59 and 5.23 (2 d, 2 H, *J* 5.8 Hz, 2 OCH), 4.70 (s, 2 H, OCH_2O), 5.34 (br.s, 1 H, NCH), 5.58 (br.s, 1 H, –CH=), 6.34 (d, 1 H, *J* 7.5 Hz, –COCH=), and 6.87 (d, 1 H, *J* 7.5 Hz, –NCH=); e.i.m.s.: *m/z* 340 (M^+), 325 (M^+ – Me), 279 (M^+ – 2 Me, OMe), 221, 214, and 172.

*1-[(1*R*, 2*S*, 3*R*)-2,3-Isopropylidenedioxy-4-methoxymethyloxymethyl-4-cyclopenten-1-yl]-4-methylthio-2(1*H*)-pyrimidinone* (**16**). — To a solution of **15** (54 mg) in methanol (2.5 mL) and water (0.5 mL) was added iodomethane (45 mg), followed by the dropwise addition of M NaOH (0.18 mL) under stirring at room temperature.

After the mixture had been stirred for 1 h at ambient temperature, acetic acid was added until neutral and the solvents were evaporated under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was concentrated under reduced pressure, and the residue chromatographed in a column of silica gel with 1:1 ethyl acetate–hexane, to give **16** (50 mg, 89% yield), pale-yellow crystal which were recrystallized from 1:1 ehter–hexane to afford colorless needles, m.p. 49–51°, $[\alpha]_D^{20}$ −16° (*c* 1.12, chloroform); R_F (ethyl acetate) 0.47; ν_{max}^{KBr} 1645, 1610, 1502, 1430, 1385, and 1372 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$; Me_4Si): δ 1.35 and 1.44 [2 s, 6 H, $C(CH_3)_2$], 2.56 (s, 3 H, SMe), 3.40 (s, 3 H, OMe), 4.29 (br.s, 2 H, CH_2O), 4.62 and 5.23 (2 d, 2 H, *J* 5.7 Hz, 2 OCH), 4.70 (s, 2 H, OCH_2O), 5.42 (t, 1 H, *J* 1.7 Hz, NCH), 5.60 (br.s, 1 H, –CH=), 6.16 (d, 1 H, *J* 7.1 Hz, NCH=C*H*–), and 7.15 (d, 1 H, *J* 7.1 Hz, NC*H*=CH–); e.i.m.s.: *m/z* 354 (M^+), 339 (M^+ − Me), 293, 234, and 187.

Anal. Calc. for $C_{16}H_{22}N_2O_5S$: C, 54.22; H, 6.25; N, 7.90. Found: C, 54.62; H, 6.55; N, 7.84.

*4-Amino-1-[(1*R*, 2*S*, 3*R*)-2,3-isopropylidenedioxy-4-methoxymethyloxymethyl-4-cyclopenten-1-yl]-2(1*H*)-pyrimidinone* (**17**). — A solution of **16** (25 mg) in methanol (2 mL), was saturated with NH_3, under cooling at −78°, in a stainless steel tube. The mixture was kept for 10 h at 100–110°. The solvent was removed under reduced pressure, the residue was purified by silica gel column chromatography (19:1 dichloromethane–methanol) to afford **17** (21 mg, 91% yield), colorless crystals, m.p. 84–85°, $[\alpha]_D^{20}$ −81°(*c* 1.77, chloroform), R_F (3:4:4 ethyl acetate–ethanol–water) 0.43; λ_{max}^{MeOH} 277, λ_{min}^{MeOH} 257 nm; ν_{max}^{film} 3350, 3125, 1660, 1625, 1485, 1390, and 1215 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$; Me_4Si): δ 1.34 and 1.43 [2 s, 6 H, $C(CH_3)_2$], 3.40 (s, 3 H, OMe), 4.28 (br.s, 2 H, CH_2O), 4.58 and 5.21 (2 d, 2 H, *J* 5.7 Hz, 2 OCH), 4.70 (s, 2 H, OCH_2O), 5.36 (br.s, 1 H, NCH), 5.59 (br.s, 1 H, –CH=), 5.82 (d, 1 H, *J* 7.5 Hz, NCH=C*H*), and 7.07 (d, 1 H, *J* 7.5 Hz, NC*H*=CH–); e.i.m.s.: *m/z* 323 (M^+), 308 (M^+ − Me) 262, 204, 155, and 149.

Anal. Calc. for $C_{15}H_{21}N_3O_5 \cdot 0.5\ H_2O$: C, 54.21; H, 6.67; N, 12.64. Found: C, 54.66; H, 6.83; N, 12.49.

*4-Amino-1-[(1*R*, 2*S*, 3*R*)-2,3-dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-2(1*H*)-pyrimidinone* (**18**). — *From* **17**. A solution of **17** (43 mg) in methanol (1 mL) and 2M HCl (2 mL) was stirred for 16 h at 30–35°. Methanol was removed under reduced pressure and the residual solution applied onto a column of Amberlite CG-120 (H^+) cation-exchange resin. After washing with water until neutral, elution with 0.07M NH_4OH and evaporation under reduced pressure gave **18** (30 mg, 94% yield), amorphous powder, $[\alpha]_D^{20}$ −67.5° (*c* 1.84, methanol), R_F (3:1:1 ethyl acetate–ethanol–water) 0.19; λ_{max}^{MeOH} 279, λ_{min}^{MeOH} 259 nm; ν_{max}^{film} 3350, 3200, 1645, 1605, 1500, 1400, 1285, and 1120 cm^{-1}; ^{1}H-n.m.r. (CD_3OD, $CDCl_3$; Me_4Si): 4.04 (t, 1 H, *J* 5 Hz, OCH), 4.28 (s, 2 H, CH_2OH), 4.55 (d, 1 H, *J* 5 Hz, OCH), 5.48 (br.s, 1 H, NCH), 5.69 (s, 1 H, –CH=), 5.88 (d, 1 H, *J* 7.5 Hz, NCH=CH–), and 7.39 (d, 1 H, *J* 7.5 Hz, NC*H*=); e.i.m.s.: *m/z* 239 (M^+), 222 (M^+ − OH), 203, 192, 112 (C + 2), 111 (C + 1), and 110 (C).

From **21**. To a solution of **21** (2.04 g) in methanol (30 mL) and water (6 mL) was added iodomethane (0.3 mL), followed by dropwise addition of M NaOH (5.5 mL) under stirring in an ice bath. After the mixture had been stirred for 30 min at the same temperature, acetic acid was added until neutrality, and the mixture evaporated to dryness under reduced pressure. A solution of the residue in methanol (10 mL) was saturated with NH_3 at $-78°$ in a stainless-steel tube, and kept for 16 h at 80–90°. The solvent was evaporated under reduced pressure, and the residue dissolved in water and applied onto a column of Amberlite IR-120 (H^+) cation-exchange resin. Elution with 2% NH_4OH and evaporation of the eluent under reduced pressure gave **18** (1.20 g, 94% yield), crystallized from aqueous ethanol (810 mg), m.p. 208–212° (dec.), $[\alpha]_D^{22}$ −94.5° (*c* 0.55, water); other spectroscopic data identical with those of the compound obtained from **17**.

Anal. Calc. for $C_{10}H_{13}N_3O_4 \cdot 0.5\ H_2O$: C, 48.38; H, 5.68; N, 16.93. Found: C, 48.57; H, 5.57; N, 16.92.

*1-[(1*R*, 2*S*, 3*R*)-2,3-Diacetoxy-4-acetoxymethyl-4-cyclopenten-1-yl]-2,4(1*H*, 3*H*)-pyrimidinedione* (**20**). — A mixture of **14** (6.07 g) and acetic anhydride (40 mL) in dry pyridine (80 mL) was stirred for 5 h at room temperature. The reaction was quenched by addition of methanol under ice cooling and the solvent removed under reduced pressure. The residual syrup was chromatographed in a column of silica gel with 3:1 ethyl acetate–hexane to give **20** (8.46 g, 91% yield), colorless, m.p. 149–150°; $[\alpha]_D^{24}$ −70° (*c* 0.32, methanol); R_F (ethyl acetate) 0.51; ν_{max}^{film} 1740–1690, 1460, 1380, and 1240 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$; Me_4Si): δ 2.06 (s, 3 H, OAc), 2.12 (s, 6 H, 2 OAc), 4.68 (br.s, 2 H, $-CH_2OAc$), 5.20 (t, 1 H, *J* 6.7 Hz, OCH), 5.70–5.94 (br, 4 H, OCH, NCH, −CH=, −COCH=), 7.04 (d, 1 H, *J* 8 Hz, N–CH=), and 9.12 (br.s, 1 H, CONHCO).

Anal. Calc. for $C_{16}H_{18}N_2O_8$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.45; H, 4.83; N, 7.62.

In addition, the N^3,2′,3′,6′-tetraacetate was obtained (670 mg, 7% yield), syrup, ν_{max}^{film} 1790, 1745, 1710, 1670, 1445, 1380, and 1240 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$; Me_4Si): δ 2.04, 2.10, 2.12 (3 s, 9 H, 3 OAc) 2.54 (s, 3 H, NAc), 4.70 (br.s, 2 H, CH_2OAc), 5.21 (t, 1 H, *J* 6 Hz, OCH), 5.68–5.96 (m, 4 H, OCH, NCH, COCH=, −CH=), and 7.09 (d, 1 H, *J* 8 Hz, N–CH=); e.i.m.s.: *m/z* 408 (M^+), 366 (M^+ − OAC), 350, 349, 307, and 204.

*1-[(1*R*, 2*S*, 3*R*)-2,3-Diacetoxy-4-acetoxymethyl-4-cyclopenten-1-yl]-4-thio-2(1*H*, 3*H*)-pyrimidinone* (**21**). — A mixture of **20** (1.5 g) and P_2S_5 (3.3 g) in dry pyridine (18 mL) was stirred for 5 h at 100–110°, and then poured into ice–water. The precipitate was collected by filtration, washed with cold ethanol, and was purified by silica gel column chromatography with 1:1 chloroform–ethyl acetate to give **21** (1.3 g, 83% yield) yellow crystals, m.p. 214–215°, $[\alpha]_D^{23}$ −84.5° (*c* 0.31, 9:1 chloroform–methanol), R_F (1:1 ethyl acetate–hexane; 0.26; λ_{max} 333, (9:1 $CHCl_3$–CH_3OH) λ_{min}; 278 nm; ν_{max}^{KBr} 1740, 1690, 1625, 1465, 1380, and 1375 cm^{-1}; ^{1}H-n.m.r. [$(CD_3)SO$; Me_4Si] δ 1.99, 2.04, 2.06 (3 s, 9 H, 3 OAc), 4.64 (br.s, 2 H, CH_2OAc), 5.32 (t, 1 H, *J* 6 Hz, OCH), 5.52 (br.s, 1 H, NCH), 5.79 (d, 1 H, *J* 6 Hz, OCH), 6.05

(s, 1 H, -CH=), 6.30 (d, *J* 8 Hz, 1 H, CSCH=), and 7.38 (d, *J* 8 Hz, 1 H, N-CH=); e.i.m.s.: *m/z* 382 (M^+), 322 (M^+ - AcOH), 262, 255, 220, and 153.

Anal. Calc. for $C_{16}H_{18}N_2O_7S$: C, 50.26; H, 4.74; N, 7.33. Found: C, 50.24; H, 4.90; N, 7.37.

1-[(1R, 2S, 3R)-2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-2-oxo-4-thiopyrimidine (**22**). — Compound **21** (1.70 g) was treated with saturated methanolic NH_3 for 1 day at room temperature. The solvent was then evaporated off under reduced pressure and the residue chromatographed in a column of silica gel with 4:1 chloroform–methanol to give **22** (950 mg, 83% yield), yellow foam, $[\alpha]_D^{21}$ −96.5° (*c* 0.19, methanol), R_F (3:1:1 ethyl acetate–ethanol–water) 0.68; λ_{max}^{MeOH} 336, 249 nm; ν_{max}^{KBr} 3350, 1690, 1610, 1460, 1260, and 1180 cm^{-1}; ^{1}H-n.m.r. (D_2O; DSS): δ 4.18 (t, *J* 5.5 Hz, 1 H, OCH), 4.30 (br.s, 2 H, CH_2OH), 4.63 (d, 1 H, *J* 5.5 Hz, OCH), 5.46 (br.s, 1 H, NCH), 5.81 (s, 1 H, CH=), 6.50 (d, 1 H, *J* 8 Hz, -CSCH=), and 7.33 (d, 1 H, *J* 8 Hz, N-CH=); e.i.m.s.: *m/z* 258 (M^+ + 2), 256 (M^+), 149, 129 (4-thioU + 1), and 128.

(1R, 2S, 3R)-2,3-Isopropylidenedioxy-1-[N-(3-methoxy-2-methylacryloyl) ureido]-4-methoxymethyloxymethyl-4-cyclopentene (**23**). — A solution of **3** (2.29 g) in dry *N,N*-dimethylformamide (50 mL) was cooled to −45 to −50° in a dry ice–acetone bath. A solution of 3-methoxy-2-methylacryloyl isocyanate [prepared from 3-methoxy-2-methylacryloyl chloride (1.35 g) and AgNCO (3.00 g) in dry benzene by heating] was added dropwise under an Ar atmosphere. The mixture was stirred for 30 min at the same temperature and then for 1 h at room temperature, poured into ice-cold, satd. $NaHCO_3$ with vigorous stirring, and extracted with ethyl acetate several times. The combined organic layer was washed with water, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The residue was chromatographed in a column of silica gel with 2:1 ethyl acetate–hexane to give **23** (3.22 g, 87% yield), colorless syrup, R_F (1:1 ethyl acetate–hexane) 0.15; ν_{max}^{film} 3250, 2940, 1680, 1610, 1530, 1470, 1370, and 1300 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$; Me_4Si): δ 1.32 and 1.38 [2 s, 6 H, $C(CH_3)_2$], 1.76 (d, *J* 1.2 Hz, 3 H, CH_3C), 3.37 (s, 3 H, OMe), 3.86 (s, 3 H, *Me*O-CH=), 4.17 (s, 2 H, CH_2O), 4.55 and 5.12 (2 d, 2 H, *J* 5.6 Hz, 2 OCH), 4.67 (s, 2 H, OCH_2O), 4.77 (m, 1 H, NCH), 5.67 (br.s, 1 H, -CH=), 7.38 (d, 1 H, *J* 1.2 Hz, MeO-C*H*=), 8.36 (br.s, 1 H, CONHCO), and 8.65 (br.d, 1 H, CHN*H*CO); f.a.b.m.s.: *m/z* 371 (MH^+).
CHN*H*CO); f.a.b.m.s.: *m/z* 371 (MH^+).

1-[(1R, 2S, 3R)-2,3-Isopropylidenedioxy-4-methoxymethyloxymethyl-4-cyclopenten-1-yl]-5-methyl-2,4(1H, 3H)-pyrimidinedione (**24**). — To a solution of **23** (3.0 g) in acetone (75 mL) was added 2.8% NH_4OH (225 mL), and the mixture stirred with reflux for 15 h. The reaction was monitored by t.l.c. (1:1 ethyl acetate–hexane). After being cooled to room temperature, the mixture was evaporated under reduced pressure and the residue coevaporated to dryness with ethanol under reduced pressure several times. The residual syrup was chromatographed in a column of silica gel with 4:1 ethyl acetate–hexane to give **24** (2.17 g, 80% yield), colorless crystals, recrystallized from 1:1 ethyl acetate–ether, m.p. 139–140.5°, $[\alpha]_D^{24}$

$-77.5°$ (*c* 1.37, chloroform); λ_{max}^{MeOH} 270 nm; ν_{max}^{KBr} 3170, 3050, 1690, 1650, 1480, 1460, 1380, 1370, and 1250 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$; Me_4Si) 1.35 and 1.44 [2 s, 6 H, $C(CH_3)_2$], 1.90 (d, 3 H, *J* 1.2 Hz, CH_3–C=), 3.41 (s, 3 H, OMe), 4.30 (s, 2 H, CH_2O), 4.59 (d, 1 H, *J* 5.6 Hz, OCH), 4.72 (s, 2 H, OCH_2O), 5.24 (d, 1 H, *J* 5.6 Hz, OCH), 5.38 (s, 1 H, NCH), 5.60 (br.d, 1 H, –CH=), 6.84 (d, 1 H, *J* 1.2 Hz, NCH=), and 9.00 (br, 1 H, CONHCO); f.a.b.m.s.: *m/z* 339 (MH^+).

Anal. Calc. for $C_{16}H_{22}N_2O_6$: C, 56.79; H, 6.55; N, 8.28. Found: C, 57.17; H, 7.10; N, 8.71.

*1-[(1*R*, 2*S*, 3*R*)-2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-5-methyl-2,4(1*H*, 3*H*)-pyrimidinone* (**25**). — A solution of **24** (4.55 g) in trifluoroacetic acid (45 mL) and water (45 mL) was stirred for 3 h at 60°, and then for 13 h at room temperature. The mixture was evaporated and coevaporated to dryness with ethanol under reduced pressure several times. The residue was dissolved in a minimum amount of methanol, the solution mixed with silica gel (20 g), and the mixture dried under reduced pressure and placed on top of a column of silica gel which was developed with 5:1 chloroform–methanol. Evaporation of the eluate under reduced pressure afforded **25** (2.55 g, 75%), crystals recrystallized from aqueous ethanol, m.p. 210–211.5° (dec.); $[\alpha]_D^{24}$ $-108°$ (*c* 0.65, methanol); R_F (5:1 chloroform–methanol) 0.17; $\lambda_{max}^{H_2O}$ 273 nm; ν_{max}^{KBr} 3400, 3050, 1680, 1480, 1400, and 1270 cm^{-1}; ^{1}H-n.m.r. [$(CD_3)_2SO$–D_2O; Me_4Si]: δ 1.76 (d, 3 H, *J* 1.0 Hz, CH_3–C=), 3.89 (d, *J* 5.6 Hz, OCH), 4.07 (s, 2 H, CH_2OH), 4.31 (d, 1 H, *J* 5.6 Hz, OCH), 5.33 (m, 1 H, NCH), 5.48 (d, 1 H, *J* 1.71 Hz, –CH=), 7.16 (d, 1 H, *J* 1.0 Hz, NCH=), and 11.21 (br.s, 1 H, CONHCO); f.a.b.m.s.: *m/z* 255 (MH^+).

Anal. Calc. for $C_{11}H_{14}N_2O_5$: C, 51.96; H, 5.55; N, 11.02. Found: C, 51.47; H, 5.80; N, 11.06.

*9-[(1*R*, 2*S*, 3*R*)-2-Hydroxy-3,6-*O*-(tetraisopropyldisiloxane-1,3-diyl)-4-cyclopenten-1-yl]guanine* (**26**). — To a solution of **9** (20.3 mg) and imidazole (22 mg) in dry *N,N*-dimethylformamide (1 mL) was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (25 μL) under cooling in an ice bath. After the mixture had been stirred for 1 h at room temperature, water was added for quenching the reaction. The precipitate was collected by filtration and partitioned between chloroform and water. The organic layer was evaporated to dryness under reduced pressure and the residue chromatographed in a silica gel column with 30:1 chloroform–methanol to give **26** (22 mg, 58% yield), colorless solid, $[\alpha]_D^{24}$ $-57.5°$ (*c* 0.45, methanol), R_F (5:1 chloroform–methanol) 0.57; ν_{max}^{KBr} 2950, 2870, 1690, 1630, 1600, 1470, 1370, and 1090 cm^{-1}; ^{1}H-n.m.r. [$(CD_3)_2SO$; Me_4Si]: δ 1.1 (br.s, 28 H, 4 $C(CH_3)_2$], 4.20 (m, 1 H, OCH), 4.43 (br.s, 2 H, CH_2O), 4.77 (d, 1 H, *J* 5.0 Hz, OCH), 5.16 (d, 1 H, *J* 6.0 Hz, NCH), 5.78 (br.s, 1 H, –CH=), 6.36 (br, 2 H, NH_2), and 7.62 (s, 1 H, NCH=); f.a.b.m.s.: *m/z* 522 (MH^+).

*9-[(1*R*, 3*R*)-3,6-O-(Tetraisopropyldisiloxane-1,3-diyl)-4-cyclopenten-1-yl] guanine* (**28**). — To a solution of **26** (246 mg) in dry acetonitrile (150 mL) was added *N,N'*-thiocarbonyldiimidazole (130 mg). The mixture was stirred with reflux for 6 h under an Ar atmosphere, and then evaporated to dryness. To the residue, dissolved in dry benzene (150 mL), were added tributyltin hydride (0.5 mL) and a catalytic

amount of azo(isobutyronitrile), and the mixture was refluxed for 5 h under an Ar atmosphere. Evaporation under reduced pressure gave a syrup, which was chromatographed in a silica gel column with 20:1 chloroform–methanol to give **28** (95 mg, 40% yield), amorphous solid, $[\alpha]_D^{24}$ −74° (*c* 0.32, methanol), R_F (10:1 chloroform–methanol) 0.33; ν_{max}^{KBr} 2850, 2880, 1700, 1630, 1600, 1470, 1370, and 1100 cm^{-1}; ^{1}H-n.m.r. [$CDCl_3$–$(CD_3)_2SO$; Me_4Si]: δ 1.1 [br.s, 28 H, 4 $C(CH_3)_2$], 2.32 (m, 2 H, CH_2), 4.46 (br.s, 2 H, CH_2O), 5.20–5.50 (m, 2 H, NCH, OCH), 5.79 (br.s, 1 H, –CH=), 6.03 (br, 2 H, NH_2), 7.73 (s, 1 H, NCH=), and 10.53 (br, 1 H, CONH); e.i.m.s.: *m/z* 506 (MH^+).

*9-[(1*R*, 3*R*)-3-Hydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]guanine* (**29**). — To a solution of **28** (80 mg) in oxolane (20 mL) was added M tetrabutylammonium fluoride in oxolane (0.4 mL). The mixture was stirred for 10 min at room temperature and evaporated under reduced pressure. A solution of the residue in methanol was applied to silica gel plates which were developed in 3:1:1 ethyl acetate–ethanol–water. Elution of the main band with 1:1 chloroform–methanol gave **29** (35 mg, 85% yield) as crystals, recrystallized from methanol, m.p. >250° (dec.); $[\alpha]_D^{24}$ −65° (*c* 0.05, methanol); R_F (3:1:1 ethyl acetate–ethanol–water) 0.47; $\lambda_{max}^{H_2O}$ 253, $\lambda_{min}^{H_2O}$ 227 nm; ^{1}H-n.m.r. $(CD_3)_2SO$; Me_4Si): δ 2.0–2.3 (m, 2 H, CH_2), 4.14 (s, 2 H, CH_2OH), 4.7–5.1 (m, 3 H, OCH, 2 OH), 5.39 (m, 1 H, NCH), 5.70 (d, 1 H, *J* 1.0 Hz, –CH=), 6.44 (br, 2 H, NH_2), 7.49 (s, 1 H, NCH=), and 10.57 (br, 1 H, CONH); c.i.m.s.: *m/z* 264 (MH^+).

*1-[(1*R*, 2*S*, 3*R*)-2-Hydroxy-3,6-O-(tetraisopropyldisiloxane-1,3-diyl)-4-cyclopenten-1-yl]-2,4(1*H*, 3*H*)-pyrimidinedione* (**30**). — To a solution of **12** (4.1 g) and imidazole (5.0 g) in dry *N,N*-dimethylformamide (77 mL) was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (4.0 mL) under cooling in an ice bath. After the mixture had been stirred for 30 min at the same temperature, additional 1,3-dichloro-1,1,3,3,-tetraisopropyldisiloxane (1.2 mL) was added. The mixture was stirred for 1 h at room temperature, and then poured into ice–water with vigorous stirring and extracted with chloroform several times. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by chromatography in a silica gel column with 3:1 chloroform–ethyl acetate to give **30** (5.85 g, 71% yield), foam, R_F (2:1 ethyl acetate–chloroform) 0.37; ^{1}H-n.m.r. ($CDCl_3$; Me_4Si): δ 1.09 [br.s, 28 H, 4 $C(CH_3)_2$], 4.07 (m, 1 H, OCH), 4.46 (br.s, 2 H, CH_2OH), 5.01 (d, 1 H, *J* 5.8 Hz, OCH), 5.43 (br.s, 1 H, NCH), 5.58 (br.s, 1 H, –CH=), 5.71 (d, 1 H, *J* 8.1 Hz, COCH=), 7.08 (d, 1 H, *J* 8.1 Hz, NCH=), and 8.74 (br, 1 H, CONHCO); f.a.b.m.s.: *m/z* 483 (MH^+).

*1-[(1*R*, 2*S*, 3*R*)-2-Hydroxy-5-methyl-3,6-O-(tetraisopropyldisiloxane-1,3-diyl)-4-cyclopenten-1-yl]-2,4(1*H*, 3*H*)-pyrimidinedione* (**31**). — To a solution of **25** (1.03 g) and imidazole (1.74 g) in dry *N,N*-dimethylformamide (25 mL) was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (1.85 g) in dry *N,N*-dimethylformamide (5 mL) with exclusion of moisture under cooling in an ice bath. The mixture was stirred for 1 h at room temperature. After quenching of the reaction by addition of water, the supernatant was removed by decantation. The residue was partitioned

between chloroform and water, and the organic layer was dried (Whatman 1PS filter paper) and evaporated under reduced pressure. The residue was purified by chromatography in a silica gel column with 4:1 chloroform–ethyl acetate to give **31** (1.35 g, 68% yield), syrup which crystallized from ethanol, m.p. 206–209°, $[\alpha]_D^{24}$ −14.5° (*c* 0.45, chloroform), R_F (2:1 chloroform–ethyl acetate) 0.33; ν_{max}^{KBr} 3450, 2950, 2880, 1700, 1470, 1390, 1380, 1260, 1100, and 1040 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$; Me_4Si): δ 1.07 [br.s, 28 H, 4 $C(CH_3)_2$], 1.90 (d, 3 H, *J* 1.2 Hz, $CH_3C=$), 4.06 (m, 1 H, OCH), 4.47 (br.s, 2 H, CH_2O), 5.01 (d, 1 H, *J* 5.4 Hz, OCH), 5.45 (m, 1 H, NCH), 5.58 (br.s, 1 H, –CH=), 6.88 (d, 1 H, *J* 1.2 Hz, NCH=), and 8.72 (br., 1 H, CONHCO); c.i.m.s.: *m/z* 497 (MH^+).

Anal. Calc. for $C_{23}H_{40}N_2O_6Si_2$: C, 55.61; H, 8.12; N, 5.64. Found: C, 55.74; H, 8.22; N, 5.29.

*1-[(1*R*, 3*R*)-3,6-O-(Tetraisopropyldisiloxane-1,3-diyl)-4-cyclopenten-1-yl]-2,4(1*H*, 3*H*)-pyrimidinedione (***34***) and 1-[(1*R*, 2*R*, 3*R*)-2-2′-anhydro-3,6-O-(tetraisopropyldisiloxane-1,3-diyl)-4-cyclopenten-1-yl]-4(1*H*)-pyrimidinone* (**38**). — (*a*). A mixture of **31** (2.13 g) and *N,N′*-thiocarbonyldiimidazole (1.73 g, 1.1 equiv.) in dry acetonitrile (50 mL) was refluxed for 3 h under an Ar atmosphere. Tributyltin hydride (9.51 mL, 4 equiv.) and a catalytic amount of azo(isobutyronitrile) were added, and the mixture refluxed for 1 h. The reaction was monitored by t.l.c. with 2:1 chloroform–ethyl acetate. The mixture was evaporated under reduced pressure and the residue chromatographed in a column of silica gel, developed with 4:1 hexane–ethyl acetate to afford **34** (920 mg, 44.7% yield), colorless syrup which crystallized from ethanol, m.p. 160–163°, $[\alpha]_D^{22}$ −92° (*c* 0.08, chloroform), R_F (2:1 ethyl acetate–chloroform) 0.5; λ_{max}^{MeOH} 267, λ_{min}^{MeOH} 233 nm; ν_{max}^{KBr} 2950, 2870, 1693, 1620, 1465, and 1380 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$; Me_4Si): δ 1.06 [br.s, 28 H, 4 $C(CH_3)_2$], 2.06 and 2.44 (ddd, 1 H, *J* 4,7,14 Hz; ddd, 1 H, *J* 4,8,14 Hz, CH_2), 4.44 (br.s, 2 H, CH_2O), 5.20 (br, 1 H, HCOSi), 5.56 (s, 1 H, –CH=), 5.70 (dd, 1 H, *J* 1.8 Hz, COCH=), 5.80 (br, 1 H, NCH), 7.09 (d, 1 H, *J* 8 Hz, NCH=), and 9.60 (br, 1 H, CONHCO); e.i.m.s.: *m/z* 466 (M^+), 426, 425, 424, and 423 [M^+ − $C(CH_3)_2$].

Anal. Calc. for $C_{22}H_{38}N_2O_5Si_2$: C, 56.62; H, 8.21; N, 6.00. Found: C, 56.51; H, 8.07; N, 6.06.

Further elution with 30:1 chloroform–methanol gave **37** (607 mg, 30% yield), m.p. 201–203°, $[\alpha]_D^{24}$ −226° (*c* 0.36, chloroform), R_F (2:1 chloroform–ethyl acetate) 0.07; λ_{max}^{MeOH} 256, 227 nm; 3450, 2950, 2880, 1660, 1530, 1480, 1260, 1110, and 1040 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$; Me_4Si): δ 1.12 [br.s, 28 H, 4 $C(CH_3)_2$], 4.42 (br.s, 2 H, CH_2O), 5.21–5.42 (m, 3 H, NCH, 2 OCH), 5.82 (br.s, 1 H, –CH=), 6.02 (d, 1 H, *J* 7.6 Hz, COCH=), and 7.29 (d, 1 H, *J* 7.6 Hz, NCH=); f.a.b.m.s.: *m/z* 465 (MH^+).

(*b*). A mixture of **30** (508 mg) and *N,N′*-thiocarbonyldiimidazole (188 mg) in dry acetonitrile (30 mL) was refluxed for 2 h under an Ar atmosphere. Additional *N,N′*-thiocarbonyldiimidazole (188 mg) was added, and refluxing was continued for 3 h. The mixture was cooled to ambient temperature, the solvent removed by evaporation under reduced pressure with exclusion of moisture, and the residue

dissolved in dry benzene (40 mL). Butyltin hydride (2.84 mL) and a catalytic amount of azo(isobutyronitrile) were added at 80°, the mixture was stirred for 1 h at 80°, and the solvent removed under reduced pressure. Compound **34** (387 mg, 79% yield) was obtained by chromatography of the residue in a column of silica gel with 6:1 chloroform–ethyl acetate.

*5-Methyl-1-[(1*R*, 3*R*)-3,6-O-(tetraisopropyldisiloxane-1,3-diyl)-4-cyclopenten-1-yl]-2,4(1*H*, 3*H*)-pyrimidinedione* (**35**). — A solution of **31** (1.90 g) and *N,N'*-thiocarbonyldimidazole (818 mg, 1.2 equiv.) in dry acetonitrile (50 mL) was refluxed for 3 h under an Ar atmosphere. Additional *N,N'*-thiocarbonyldiimidazole (545 mg, 0.8 equiv.) was added and refluxing continued for 3 h. The mixture was evaporated to dryness under reduced pressure with exclusion of moisture, and the residue dissolved in dry benzene (150 mL). Butyltin hydride (9.80 mL) and a catalytic amount of azo(isobutyronitrile) were added at 80°, the mixture stirred for 1.5 h at the same temperature, and the solvent removed under reduced pressure. The residue was chromatographed in a column of silica gel with 6:1 chloroform–ethyl acetate to give **35** (1.40 g, 77% yield), syrup which crystallized from ethanol, m.p. 162–164°, $[\alpha]_D^{24}$ +5.2° (*c* 0.27, chloroform), R_F (2:1 chloroform–ethyl acetate) 0.26; ν_{max}^{KBr} 3440, 2950, 2870, 1690, 1470, 1380, 1260, 1100, and 1030 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$;Me_4Si): δ 1.07 [br.s, 28 H, 4 $C(CH_3)_2$], 1.89 (d, 1 H, *J* 1.2 Hz, $CH_3C=$), 2.12 and 2.35 (2 m, 2 H, CH_2), 4.46 (br.s, 2 H, CH_2O), 5.21 (m, 1 H, OCH), 5.57 (br.s, 1 H, –CH=), 5.76 (m, 1 H, NCH), 6.89 (d, *J* 1.2 Hz, 1 H, NCH=), and 8.98 (br.s, 1 H, CONHCO); c.i.m.s.: *m/z*.

Anal. Calc. for $C_{23}H_{40}N_2O_5Si_2$: C, 57.46; H, 8.39; N, 5.83. Found: C, 57.39; H, 8.46; N, 5.49.

*1-[(1*R*, 3*R*)-3-Hydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-2,4(1*H*, 3*H*)-pyrimidinedione* (**36**). — To a solution of **34** (985 mg) in oxolane (35 mL) was added M tetrabutylammonium fluoride (5.1 mL) in oxolane. The mixture was stirred for 30 min at room temperature and then evaporated under reduced pressure. The residue was partitioned between chloroform and water. The aqueous layer was separated and evaporated under reduced pressure. A chromatographic purification in a column of silica gel with 10:1 chloroform–methanol afforded **36** (353 mg, 71% yield), foam which was crystallized from ethanol, m.p. 147–149°, $[\alpha]_D^{24}$ −46° (*c* 0.36, methanol, R_F (5:1 chloroform–methanol) 0.23; $\lambda_{max}^{H_2O}$ 268 nm; ν_{max}^{KBr} 3400, 3170, 1700, 1470, 1420, 1400, 1280, and 1250 cm^{-1}; ^{1}H-n.m.r. [$(CD_3)SO$; Me_4Si]: δ 1.80–2.29 (m, 2 H, CH_2), 4.12 (d, *J* 4.0 Hz, CH_2OH), 4.65–4.88 (m, 3 H, OCH, 2 OH), 5.49–5.57 (m, 3 H, NCH, –CH=, COCH=), 7.20 (d, 1 H, *J* 7.8 Hz, NCH=), and 11.04 (br, 1 H, CONHCO); c.i.m.s.: *m/z* 225 (MH^+).

Anal. Calc. for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.50. Found: C, 53.33; H, 5.68; N, 12.81.

*1-[(1*R*, 3*R*)-3-Hydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-5-methyl-2,4-(1*H*, 3*H*)-pyrimidinedione* (**37**). — A mixture of **35** (97 mg) and M tetrabutylammonium fluoride in oxolane (0.42 mL) was treated in a manner similar to that just described. A chromatographic purification by preparative t.l.c. with 5:1 chloro-

form–methanol gave **37** (44 mg, 92% yield) as colorless crystals which were recrystallized from aqueous ethanol, m.p. >210° (dec.), $[\alpha]_D^{24}$ −31° (*c* 0.42, methanol), R_F (5:1 chloroform–methanol) 0.33; $\lambda_{max}^{H_2O}$ 272, $\lambda_{max}^{H^+}$ 272, $\lambda_{max}^{OH^-}$ 270 nm; ν_{max}^{KBr} 3380, 3170, 3030, 1680, 1480, 1290, and 1260 cm^{-1}; ^{1}H-n.m.r. [$(CD_3)SO$; Me_4Si]: δ 1.75 (d, 3 H, *J* 1.2 Hz, MeC=), 1.9–2.1 (m, 2 H, CH_2), 4.11 (d, 2 H, *J* 5.0 Hz, CH_2OH), 4.75 (m, 1 H, OCH), 5.53 (m, 2 H, NCH, -CH=), and 7.07 (d, 1 H, *J* 1.2 Hz, NCH=); c.i.m.s.: *m/z* 239 (MH^+).

Anal. Calc. for $C_{11}H_{14}N_2O_4 \cdot 2/3H_2O$: C, 52.58; H, 6.55; N, 11.15. Found: C, 52.78; H, 6.00; N, 11.39.

*1-[(1*R*, 2*R*, 3*R*)-2,2'-Anhydro-3-hydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-4(1*H*)-pyrimidinone* (**39**). — Treatment of **38** (460 mg) as just described gave **39** (224 mg, quantitative yield), $[\alpha]_D^{24}$ −171° (*c* 0.23, methanol), R_F (5:1 chloroform–methanol) 0.10; $\lambda_{max}^{H_2O}$ 257, 225 nm; ν_{max}^{KBr} 3400, 3220, 1650, 1620, 1520, 1480, 1250, 1230, and 1100 cm^{-1}; ^{1}H-n.m.r. [$(CD_3)SO$; Me_4Si]: δ 4.09 (br.s, 2 H, CH_2O), 4.72 (br.s, 1 H, OCH), 5.12 (d, 1 H, *J* 7.1 Hz, OCH), 5.76 (d, 1 H, *J* 7.3 Hz, COCH=), 5.87 (d, 1 H, *J* 1.0 Hz, -CH=), and 7.76 (d, *J* 7.3 Hz, NCH=); c.i.m.s.: *m/z* 223 (MH^+).

*1-[(1*R*, 3*R*)-3-Acetoxy-4-acetoxymethyl-4-cyclopenten-1-yl]-2,4(1*H*, 3*H*)-pyrimidinedione* (**40**). — A mixture of **36** (1.44 g) and acetic anhydride (15 mL) in dry pyridine (30 mL) was stirred for 16 h at ambient temperature. After quenching of the reaction by addition of methanol under cooling in an ice bath, the solvent was removed under reduced pressure. The residue was partitioned between chloroform and water, and the organic layer separated, dried (Whatman 1PS filter paper), and concentrated under reduced pressure. The residue was purified by chromatography in a silica gel column with ethyl acetate–hexane, and then ethyl acetate to give **40** (1.74 g, 88% yield), colorless foam, $[\alpha]_D^{22}$ −54° (*c* 0.24, methanol), R_F (ethyl acetate) 0.42; λ_{max}^{MeOH} 267, λ_{min}^{MeOH} 232.5 nm; ν_{max}^{KBr} 1740, 1690, 1460, 1375, and 1235 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3/Me_4Si$): δ 2.08 and 2.12 (2 s, 6 H, 2 OAc), 2.20 and 2.52 (m, 2 H, CH_2), 4.73 (br.s, 2 H, CH_2OAc), 5.76 (d, 1 H, *J* 8 Hz, COCH=), 5.90 (br, 3 H, CHOAc, NCH, -CH=), 7.05 (d, 1 H, *J* 8 Hz, NCH=), and 9.76 (br, 1 H, CONHCO); e.i.m.s.: *m/z* 309 ($M^+ + 1$), 308 (M^+), 249 ($M^+ - OAc$), 248 ($M^+ -$ AcOH), 206, and 205.

*1-[(1*R*, 3*R*)-3-Acetoxy-4-acetoxymethyl-4-cyclopenten-1-yl]-2-oxo-4-thiopyrimidine* (**41**). — To a solution of **40** (1.70 g) in pyridine (20 mL) was added P_2S_5 (4.40 g), and the mixture stirred for 5 h at 100–110°. Compound **42** (1.55 g, 87% yield) was obtained in the same manner as described before for **20** from **21**, pale yellow foam, $[\alpha]_D^{22}$ −36° (*c* 0.22, methanol); R_F (1:1 ethyl acetate–hexane) 0.39; λ_{max}^{MeOH} 335, λ_{min}^{MeOH} 277.5 nm; ν_{max}^{KBr} 1740, 1710, 1615, 1455, 1370, 1235, and 1135 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$; Me_4Si): δ 2.08 and 2.12 (2 s, 6 H, 2 OAc), 2.22 and 2.54 (m, 2 H, CH_2), 4.72 (br.s, 2 H, CH_2OAc), 5.88 (br, 3 H, NCH, OCH, -CH=), 6.40 (dd, 1 H, *J* 2.8 Hz, CSCH=), 6.86 (d, 1 H, *J* 8 Hz, NCH=), and 10.10 (br.s, 1 H, CONHCS); e.i.m.s.; *m/z* 326 ($M^+ + 2$), 324 (M^+), 204 ($M^+ - 2$ AcOH), 197, 137, and 95.

*4-Amino-1-[(1*R*, 3*R*)-3-hydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-2(1*H*)-*

pyrimidinone (**42**). — To a solution of **41** (1.35 g) in methanol (20 mL) and water (5 mL) was added iodomethane (2 mL), and M NaOH (4.5 mL) was added dropwise under cooling in an ice bath. The mixture was stirred for 1 h at the same temperature, and then made neutral with 10% acetic acid in methanol. The solvent was removed under reduced pressure, the residue dissolved in methanol (5 mL), and liquid ammonia (15 mL) added under cooling at −78°. The mixture was kept, in a stainless steel tube, for 5 h at 90°, and then 16 h at 65°, evaporated under reduced pressure, and the residue treated with activated charcoal in methanol. The solvent was removed under reduced pressure and the residue, dissolved in dilute HCl, was applied onto a column of Amberlite CG-120 (H^+) cation-exchange resin. After washing with water, elution with 70 mM NH_4OH gave **42** (850 mg, 92% yield), slightly yellow foam which crystallized from ethanol, m.p. 188–191° (dec.), $[\alpha]_D^{22}$ −12.5° (*c* 0.22, methanol), R_F (3:1:1 ethyl acetate–ethanol–water) 0.35; λ_{max}^{MeOH} 276, λ_{min}^{MeOH} 260 nm. ν_{max}^{KBr} 3325, 3200, 1640, 1607, 1530, 1485, and 1395 cm^{-1}; ^{1}H-n.m.r. [$(CD_3)SO$; Me_4Si]: δ 1.82 and 2.12 (m, 2 H, CH_2), 4.08 (br.s, 2 H, CH_2OH), 4.68 (br.s, 1 H, *CH*OH), 5.49 (br.s, 2 H, -CH=C), NCH), 5.64 (d, 1 H, *J* 8 Hz, -*CH*=CH-N), and 7.18 (d, 1 H, *J* 8 Hz, -CH=*CH*N); e.i.m.s.: *m/z* 206 (M^+ − OH), 205 (M^+ − H_2O), 188, 187, 116, 114, 113, and 112.

Anal. Calc. for $C_{10}H_{13}N_3O_2$: C, 53.81; H, 5.87; N, 18.82. Found: C, 53.40; H, 5.77; N, 18.75.

*1-[(1*R*, 3*R*)-3-Hydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-2-oxo-4-thiopyrimidine* (**43**). — A solution of **42** (110 mg) in methanol (3 mL) was saturated with NH_3 under cooling in an ice bath. The mixture was kept in a stoppered container for 16 h at room temperature, the solvent removed under reduced pressure, and the residue purified by chromatography in a column of silica gel with 5:1 chloroform–methanol to give **43** (81 mg, quantitative yield), yellow oil, $[\alpha]_D^{22}$ −1.6° (*c* 0.8, methanol; R_F (3:1:1 ethyl acetate–ethanol–water) 0.76; λ_{max}^{MeOH} 336, λ_{min}^{MeOH} 278 nm; ν_{max}^{film} 3375, 1690, 1610, 1460, 1250, 1135, and 1070 cm^{-1}; ^{1}H-n.m.r [$(CD_3)_2SO$; Me_4Si]: δ 2.24 (m, 2 H, CH_2), 4.28 (br.s, 2 H, CH_2OH), 4.80–4.90 (br, 1 H, OCH), 5.68 (br.s, 2 H, NCH, -CH=), 6.30 (d, 1 H, *J* 8 Hz, -CSCH=), and 7.13 (d, 1 H, *J* 8 Hz, NCH=); e.i.m.s.: *m/z* 241 (M^+ + 1), 240 (M^+), 149, 129, and 128.

*1-[(1*R*, 2*R*, 3*R*)-2,2'-Anhydro-3,6-*O*-(tetraisopropyldisiloxane-1,3-diyl)-4-cyclopenten-1-yl]-4(1*H*)-pyrimidinone* (**38**). — To a solution of **30** (900 mg) and 4-dimethylaminopyridine (235 mg) in dry pyridine (5 mL) were added triethylamine (0.27 mL) and then trifluoromethanesulfonyl chloride (0.22 mL). The mixture was stirred for 2 h at room temperature, and then poured into ice–water and extracted with chloroform several times. The combined organic layer was washed with water, dried (Whatman 1PS filter paper), and evaporated under reduced pressure. The residue was chromatographed in a column of silica gel with 50:1 chloroform–methanol to give **38** (460 mg, 53% yield), identical in all respects with that obtained from **32**.

*1-[(1*R*, 2*R*, 3*R*)-2,3-Diacetoxy-4-acetoxymethyl-4-cyclopenten-1-yl]-2,4(1*H*, 3*H*)-pyrimidinedione* (**45**). — A solution of **39** (220 mg) in water (1 mL) and M

NaOH (0.5 mL) was stirred for one day at room temperature, and then for one day at 60°. After neutralization with 2M acetic acid, the solvent was removed under reduced pressure. The remaining solvent was codistilled several times with dry pyridine to afford crude **44**, which was dissolved in dry pyridine (5 mL) and acetic anhydride (0.5 mL). The mixture was stirred for 5 h at room temperature, the reaction quenched by addition of methanol, and the solvent removed under reduced pressure. The residue was partitioned between chloroform and water. The organic layer was separated, dried (Whatman 1PS), and evaporated to dryness under reduced pressure. The residue was purified by chromatography in a silica gel column with 40:1 chloroform–methanol to give **45** (355 mg, 98% yield), syrup, $[\alpha]_D^{24}$ −24.5° (*c* 0.40, methanol), R_F (20:1 chloroform–methanol) 0.27; ^{1}H-n.m.r. ($CDCl_3$; Me_4Si): δ 1.99, 2.12 and 2.13 (3 s, 9 H, 3 OAc), 4.71 (br.s, 2 H, CH_2OAc), 5,42 (t, 1 H, *J* 3.0,6.0 Hz, OCH), 5.70 (d, 1 H, *J* 8.1 Hz, COCH=), 5.6–6.0 (m, 3 H, NCH, OCH, -CH=C), 7.03 (d, 1 H, *J* 8.1 Hz, NCH=), and 9.30 (br, 1 H, CONHCO); c.i.m.s.: *m/z* 367 (MH^+) and 307 (MH^+ − AcOH).

*1-[(1*R*, 2*R*, 3*R*)-2,3-Diacetoxy-4-acetoxymethyl-4-cyclopenten-1-yl]-4-thio-2(1*H*, 3*H*)-pyrimidinone* (**46**). — To a solution of **45** (350 mg) in dry pyridine (7 mL) was added P_2S_5 (770 mg). The mixture was stirred for 4 h at 100–110°, and then poured into ice–water and extracted with chloroform several times. The combined organic layer was dried (Whatman 1PS) and evaporated under reduced pressure, and the residue chromatographed in a column of silica gel with 50:1 chloroform–methanol to give **46** (329 mg, 90% yield), pale-yellow amorphous powder, characterized only by ^{1}H-n.m.r. and used without further purification; R_F (20:1 chloroform–methanol) 0.49; ^{1}H-n.m.r. ($CDCl_3$; Me_4Si): δ 1.98 (s, 3 H, OAc), 2.10 (s, 6 H, 2 OAc), 4.70 (br.s, 2 H, CH_2OAc), 5.47 (dd, 1 H, *J* 3.0,6.0 Hz, C*H*OAc), 5.7–6.0 (m, 3 H, NCH, C*H*OAc, -CH=C), 6.37 (d, 1 H, *J* 7.0 Hz, CSCH=), and 6.87 (d, 1 H, *J* 7.0 Hz, NCH=).

*4-Amino-1-[(1*R*, 2*R*, 3*R*)-2,3-dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-2(1*H*)-pyrimidinone* (**48**). — To a mixture of **46** (320 mg) and iodomethane (0.12 mL) in methanol (15 mL) and water (3 mL) was added dropwise M NaOH (1.1 mL). After the mixture had been stirred for 1 h at room temperature, 10% acetic acid was added to the reaction mixture to neutrality. The solvent was evaporated to dryness under reduced pressure to afford crude **47**. A solution of **47** in methanol (20 mL) was saturated with NH_3 at −78° in a stainless-steel tube and kept for 9 h at 90°. It was concentrated under reduced pressure, and the residue applied to preparative silica gel plates which were developed in 1:1 chloroform–methanol. The major band was separated and eluted with 1:1 chloroform–methanol to give **48** (85 mg, 43% yield), which crystallized from methanol, m.p. >262° (dec.), $[\alpha]_D^{24}$ +49° (*c* 0.23, water), R_F (10:6:3:4 butyl acetate–acetic acid–acetone–water) 0.17; ν_{max}^{KBr} 3400, 3330, 3210, 1650, 1490, 1400, 1290, 1210, and 1030 cm^{-1}; ^{1}H-n.m.r. [$(CH_3)_2SO$–D_2O; Me_4Si]: δ 4.07 (m, 3 H, C*H*OH, CH_2OH), 4.30 (dd, 1 H, *J* 1.0, 5.4 Hz, C*H*OH), 5.50 (m, 2 H, NCH, -CH=C), 5.59 (d, *J* 7.3 Hz, -C*H*=CH-N), 6.90 (br, 2 H, NH_2), and 7.10 (d, *J* 7.3 Hz, 1 H, NCH=); c.i.m.s.: *m/z* 240 (MH^+).

Anal. Calc. for $C_{10}H_{13}N_3O_4$: C, 50.20; H, 5.48; N, 17.57. Found: C, 49.92; H, 5.50; N, 17.39.

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SYNTHESIS OF *C*-ARABINOFURANOSYL COMPOUNDS. PHOSPHONATE AND CARBOXYLATE ISOSTERES OF D-ARABINOSE 1,5-BISPHOSPHATE*

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ABSTRACT

Electrophile-mediated cyclization of 3,4,6-tri-*O*-benzyl-1,2-dideoxy-D-*arabino*-hex-1-enitol with *N*-bromosuccinimide yielded primarily 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-bromo-1-deoxy-D-glucitol (**10**). This apparently kinetically controlled reaction was of key importance in the successful synthesis of a phosphonate analog of β-D-arabinose 1,5-bisphosphate (**1**), namely, 2,5-anhydro-1-deoxy-1-phosphono-D-glucitol 6-phosphate (**4**), with high stereoselectivity. By contrast, condensation of the sodium salt of tetraethyl methylenediphosphonate and 2,3,5-tri-*O*-benzyl-D-arabinose (**7**) gave a phosphonate compound slightly enriched in the 2,5-anhydro-D-mannitol (α) isomer. In the Wittig–Michael reaction of stabilized phosphoranes with **7**, the α isomer preponderated. Since equilibration of methyl 3,6-anhydro-4,5,7-tri-*O*-benzyl-2-deoxy-D-*glycero*-D-*galacto*- (**33**) and -D-*gulo*-heptonate (**34**) (5:1) resulted in a 1:1 α:β ratio, the preference for the 2,5-anhydro-D-mannitol (α) isomer probably reflects a kinetic bias. The carbomethoxy anomers were converted independently into the α and β carboxylate isosteres (**5** and **6**, respectively) of D-arabinose 1,5-diphosphate. Empirical force field calculations (MMP2) and n.m.r. experiments were conducted on the pairs of diastereomers **9** and **10**, and **33** and **34**. The calculations predict that the α and β anomers of each pair have similar energies, differing by only 2.1 kJ/mol. Compounds **4, 5**, and **6** were evaluated for biological activity.

INTRODUCTION

Research into the synthesis and biological properties of *C*-glycosyl com-

*A preliminary communication has been published (see ref. 8).
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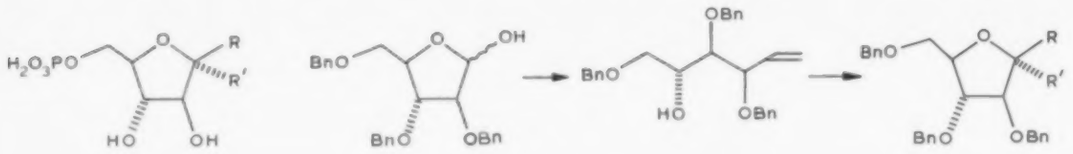


1 R = H, R′ = OPO_3H_2
2 R = OPO_3H_2, R′ = H
3 R = OPO_3H_2, R′ = CH_2OH
4 R = $CH_2PO_3H_2$, R′ = H
5 R = H, R′ = CH_2CO_2H
6 R = CH_2CO_2H, R′ = H

7

8

9 R = H, R′ = CH_2Br
10 R = CH_2Br, R′ = H
11 R = H, R′ = CH_2HgBr
12 R = CH_2HgBr, R′ = H

pounds has expanded over the last decade[1,2]. Our interest in this area arose out of a desire to obtain stable analogs of D-arabinose 1,5-bisphosphate[3] (**1**), the β anomer* of which (**2**) retains a significant portion of the biological activity of β-D-fructose 2,6-diphosphate[3,4] (**3**). Compounds **2** and **3** are activators of 6-phosphofructo-1-kinase (EC 2.7.1.11) and inhibitors of fructose 1,6-bisphosphatase (EC 3.1.3.11), important enzymes in the metabolism of D-glucose. Since the anomeric phosphate group in **2** and **3** is very prone to hydrolysis, we decided to synthesize the phosphonate and carboxylate analogs, **4–6**, as stable isosteres (for examples of the synthesis and use of phosphonates as phosphate isosteres, see refs. 5–8).

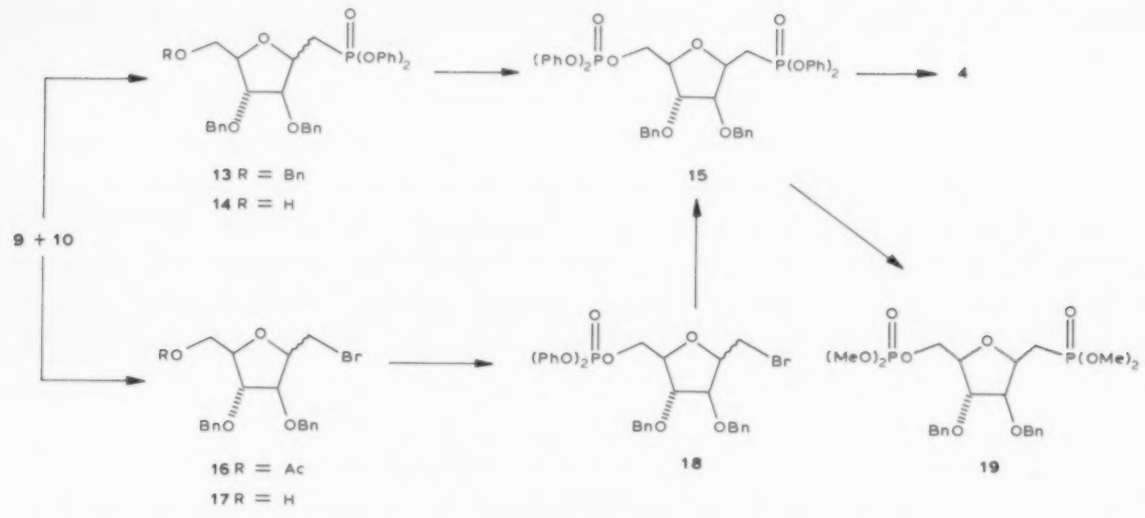
In our synthetic studies, we have prepared compounds highly or totally enriched in either *C*-β- or -α-D-arabinofuranosyl structures. Our preliminary communication[8] briefly described the synthesis of **4** in a stereoselective manner. Herein, we report the full details of this synthesis, as well as alternative approaches to the synthesis of **4** and the synthesis of the carboxylate isosteres **5** and **6**. Additionally, we have performed empirical-force-field (EFF) calculations and n.m.r. experiments on several of the *C*-D-arabinofuranosyl compounds.

RESULTS AND DISCUSSION

Phosphonate synthesis. — Condensation of the protected D-arabinose derivative **7** with 2.3 mol equiv. of methylenetriphenylphosphorane in oxolane (THF) gave the alkenol **8** in 68% yield[8]. Treatment of **8** with *N*-bromosuccinimide afforded, almost quantitatively, an 11:89 mixture of the α and β anomers **9** and **10**, respectively, which were not separable by t.l.c.[8,9]. As we have already reported[8], a similar cyclization of **8** with mercuric acetate[10] produced the mercurials **11** and **12** in an 11:89 ratio (after exchange to the bromide).

A related sequence, involving methylenetriphenylphosphorane and 2,3,4,6-tetra-*O*-benzyl-D-glucose, has been reported by Pougny *et al.*[10]. In their example,

*Throughout the paper, the term "anomer" is used in the same context for *C*-glycosyl compounds as for carbohydrates. In the Experimental section where the 2,5-anhydro-D-hexitol nomenclature is used, the α and β anomers correspond to the D-*manno* and D-*gluco* epimers, respectively.

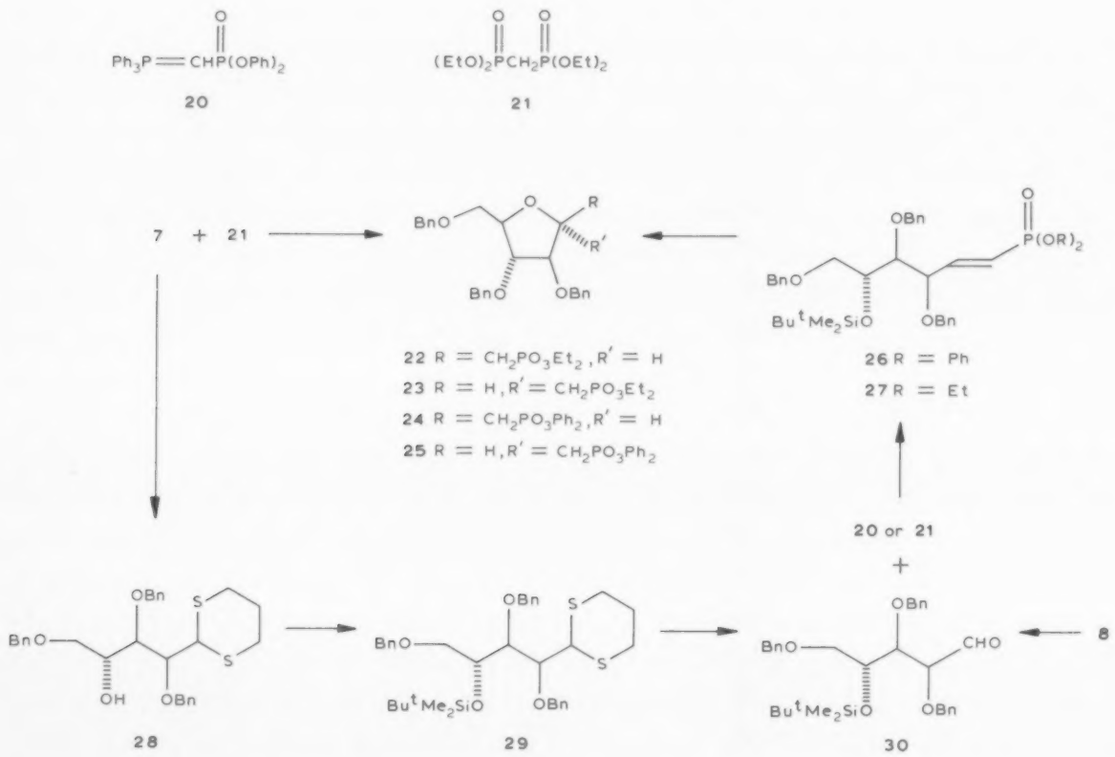


electrophile-mediated cyclization of a homologous alkenol with mercuric acetate led to a single (α) anomer. The importance of this result is that the cyclization proceeded in a manner *cis* to the proximal (originally allylic) benzyl ether substituent, an effect Pougny *et al.*[10] attributed to through-space coordination between the proximal benzyl ether and the electrophile[10,11]. We have suggested[8] that this stereoselectivity may be due to the through-bond *electronic* influence of the proximal benzyl ether, such as predicted by the "inside alkoxy" effect[12]. Several research groups have obtained similar stereochemical results for haloetherifications of allylic ethers and alcohols[13], as well as kinetic halolactonization reactions[14,15] (especially in the presence of allylic oxygen substituents).

The 11:89 mixture of **9** and **10** was transformed into **4** as follows[8]. An Arbusov reaction with diphenylethyl phosphite[16,17] gave the diphenyl phosphonate **13**. On removal of the benzyl ether groups by catalytic hydrogenolysis with palladium and hydrogen or transfer hydrogenation, considerable decomposition took place. The diphenylphosphoryl ester group of the phosphonate may have cyclized onto the free adjacent hydroxyl group in a side-reaction following debenzylation, a problem observed previously in a related system[18]. Consequently, we sought to prepare alcohol **14** from **13**. Selective deprotection with a pyridine-poisoned catalyst[3] gave a low yield of **14**. Alternatively, we treated **13** carefully with one mol equiv. of iodotrimethylsilane[19] to furnish **14** in 25–40% yield. This compound was phosphorylated conventionally to give **15** which, fortunately, is a solid, and crystallization supplied material consisting solely of the β anomer (as determined by ^{13}C n.m.r. spectrometry[8,20]). The overall yield of **15** from the mixture of **9** and **10** was around an unacceptably low 10%. Thus, we developed an alternative synthesis in which the low-yielding, selective debenzylation step (*e.g.*, **13** to **14**) was performed first. Acid-catalyzed acetolysis[22] of an 11:89 mixture of **9** and **10** produced the monoacetate **16** in 86% yield. Deacetylation gave **17**, phosphorylation of which produced the phosphate **18**, also in high yield (60% from **16**). The Arbusov reaction proceeded in the same manner as mentioned earlier, giving desired **15** in ~40%

yield. By use of this route, the total yield of **15** from the mixture of **9** and **10** was ~20%.

Deprotection of **15** proved to be more difficult than anticipated, thus, ironically, it was a major challenge in the synthesis. Lithium–ammonia reduction, which had been employed effectively by us in the synthesis of anomeric phosphates[3], resulted in extensive decomposition. Attempted hydrolysis of the phenyl phosphoryl esters also caused decomposition, and hydrogenolysis in the presence of platinum not only removed the four phenyl groups, but also led to monodebenzylation and reduction of one of the benzyl ether groups into a cyclohexylmethyl group. Initial debenzylation with 10% palladium-on-carbon proceeded slowly, and it appeared that cyclization to a *cis*-fused 1,2-oxaphospholane had again occurred, similar to the observation made in the hydrogenolysis of **13** (see above)[18]. Transfer hydrogenation (cyclohexene) went slowly as well, and the desired product was obtained in only a low yield (~10–20%). We explored the use of fluoride ion[23], which is a good nucleophile, for promoting phosphoryl ester hydrolysis. The phenyl esters were removed with cesium or tetrabutylammonium fluoride in oxolane, but all of the resultant fluorine–phosphorus bonds could not be efficiently hydrolyzed, possibly owing to the greater stability of the second P–F bond on each phosphorus atom[24]. However, conversion of **15** to the tetramethyl ester **19** in 65% yield was successfully achieved by use of cesium fluoride in refluxing methanol. The fluoride ion was essential, as **15** remained unchanged when heated in refluxing methanol. Compound **19** was stereochemically pure (β-D anomer) as shown by ^{13}C-n.m.r. spectroscopy. Hydrogenolysis of **19** with 10% palladium-on-carbon removed the



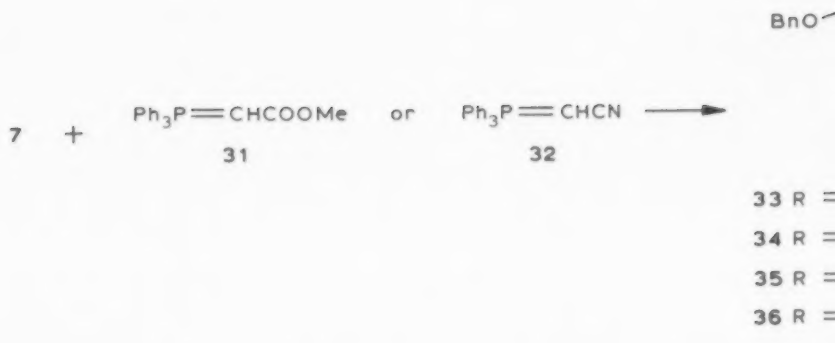
benzyl ethers, but proceeded with cyclization of the phosphonyl group onto the adjacent hydroxyl group (^{1}H-n.m.r. and mass spectral evidence). We had intended to transform **19** into **4** with iodotrimethylsilane[19]; however, this was preempted by the discovery of the following, three-step sequence to deprotect **15**. Treatment with 2.1 mol equiv. of tetramethylammonium hydroxide released two of the phenyl esters, presumably one from each phosphorus atom. At this point, the benzyl ethers were removed by hydrogenolysis without the problem of intramolecular cyclization, probably because the phosphonate group was protected as a monoanion. Finally, the phenyl esters were removed with hydrogen and platinum to give **4**, which was purified by selective precipitation as the disodium salt (34% overall yield from **15**).

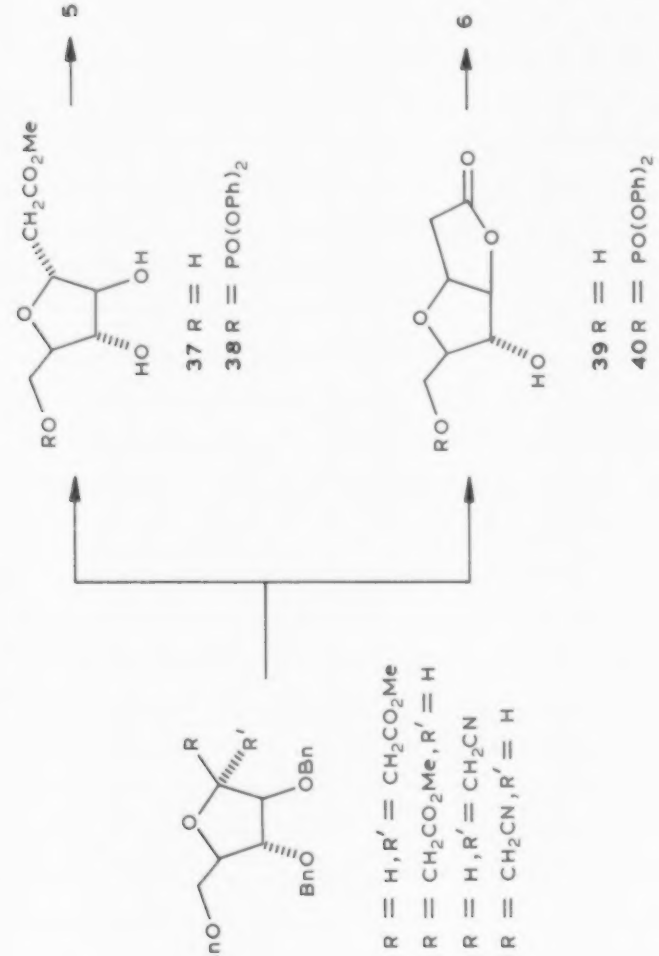
We also investigated the preparation of phosphonate intermediates directly from **7**. Attempted condensation of the stabilized phosphorane[6,21] **20** with **7** in toluene at 110° or dimethyl sulfoxide at 50° resulted in no reaction. Condensation of **7** with tetraethyl methylenediphosphonate (**21**) under alkaline, two-phase conditions[7] was unsuccessful, as well. However, **7** reacted with the anion derived from the diphosphonate **21** in a homogeneous system to give **22** and **23** in ~50% yield with an α-to-β ratio of 2:1 (these anomers were inseparable by t.l.c.)[25].

In another approach to a phosphonate intermediate, **7** was treated with 1,3-propanedithiol in the presence of methanesulfonic acid to generate the alcohol **28** (40% yield), which was protected by treatment with *tert*-butylchlorodimethylsilane to give **29** (100% yield). Testing of various methods for removal of the dithiane residue led us to employ *N*-bromosuccinimide in aqueous acetonitrile at −10°; this gave the desired compound **30** in 50–99% yield. Unfortunately, on a large scale (70 mmol of **29**), the silylated aldehyde **30** was contaminated with a considerable proportion of **7**, which could not be readily separated. We suppose that **7** was regenerated by attack of a transient thionium ion*, formed during removal of the dithiane group, on the oxygen atom of the silyl ether, followed by desilylation and hydrolysis of the anomeric thiol. Alternatively, the alkenol **8** was protected with the *tert*-butyldimethylsilyl group and subjected to ozonolysis (using a dimethyl sulfide workup) to afford **30** in 70% yield. Reaction of **30** with the stabilized ylide **20** or diphosphonate **21** gave intermediates **26** or **27**, respectively, both in yields of ~20–40%. Treatment of **27** with fluoride ion gave **22** and **23** (~25%), enriched in the α-D anomer **23** (α:β ratio was 2:1). However, treatment of **26** with fluoride ion in oxolane or ethanol, or under a number of acidic conditions, led to decomposition without formation of **24** and **25**. Although these exploratory reactions were not optimized, they demonstrated the feasibility of other approaches to phosphonate isosteres of **2**. We elected to concentrate upon the electrophile-mediated cyclization of **8** (*viz.* **8** to **10**), because it led to the β-D configuration (**4**), thought[3] to be essential for biological activity**.

*For an example of this type of reaction, see ref. 26.

McClard *et al.*[25] have described the preparation of a mixture of **4 and its 2,5-anhydro-D-mannitol epimer. This mixture had a similar potency in activating phosphofructo-1-kinase, relative to that of our sample of **4**, but was a more effective inhibitor of fructose-1,6-bisphosphatase, suggesting that 2,5-anhydro-D-mannitol epimer may be a potent inhibitor of this latter enzyme.


BnO
7
+
Ph3P=CHCOOMe
31
or
Ph3P=CHCN
32
33 R =
34 R =
35 R =
36 R =


5
6
37 R = H
38 R = PO(OPh)2
39 R = H
40 R = PO(OPh)2
R = H, R′ = CH2CO2Me
R = CH2CO2Me, R′ = H
R = H, R′ = CH2CN
R = CH2CN, R′ = H

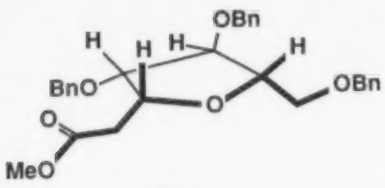
Carboxylate synthesis. — The synthesis of **5** and **6** originated in the reaction of **7** with stabilized phosphorane **31**, in the manner of Ohrui *et al.*[20]. Refluxing 2 mol equiv. of **31** with **7** for 10 h produced a 9:1 mixture of **33** and **34**. Cyclization occurred spontaneously, since no open-chain alkenes were detected. In different experiments, the ratio of **33** to **34** varied from 9:1 to 5:1. This suggested that the thermodynamic ratio is different from 9:1. Indeed, equilibration[20] of a 5:1 mixture of **33** and **34** produced a final ratio of 1:1. Thus, there is no thermodynamic preference for either isomer of this pair of diastereomers. Treatment of **7** with phosphorane[27] **32** produced a mixture of nitriles **35** and **36** in a ratio of 2:1. This reaction also favors the α-D anomer (**35**), as in the reaction of **7** with **31**. Treatment of the mixture of **35** and **36** with base caused the facile elimination of benzyl alcohol, similar to some recently reported observations[28]. A 9:1 mixture of **33** and **34** was hydrogenolyzed to give a mixture of, preponderantly, methyl ester **37**, along with lactone **39**. The formation of lactone **39** from **34** supports the stereochemical assignment of **34**, which was based on ^{13}C-n.m.r. data*. Compounds **37** and **39** were easily separated by chromatography on silica gel, and each was selectively phosphorylated to give compounds **38** and **40**, respectively. A two-stage deprotection of **38** and **40** by use of platinum and hydrogen for the phenyl esters, and then basic hydrolysis of the carboxylic esters gave **5** and **6**, respectively, characterized as their trisodium salts.

Force-field calculations and n.m.r. experiments. — Since oxolane-ring systems are conformationally fluxional, it is not obvious *a priori* which (if any) tri-*O*-benzylarabinofuranosyl anomer is more thermodynamically stable, a point which might have relevance to the mechanistic analysis of the reactions discussed above. We conducted EFF calculations in order to address this question. Such calculations give information not only on the preferred conformation for a molecule, but also on alternative conformations that may be adopted. The degree to which various low-energy conformations contribute can be readily ascertained by inspection of the calculated energies (for a related study, see Burkert *et al.*[30]).

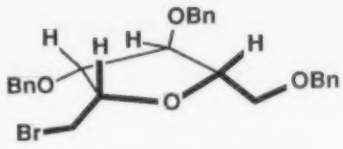
Force-field calculations for the bromomethyl compounds **9** and **10**, and esters **33** and **34**, were conducted with the MMP2 program developed by Burkert and Allinger[31]. Two low-energy conformations were found for both of the α anomers **9** and **33**, but only one reasonable conformation was obtained for the β anomers **10** and **34**. These conformations are displayed in Fig. 1, and the calculated energies, dihedral angles for the ring protons, and calculated vicinal, proton–proton coupling constants based on the dihedral angles, in Table I.

The energy minima were found after considerable analysis of possible ring conformations and conformational orientations accessible to the substituents (some details are mentioned in the Experimental section). The low-energy conformations generally have the majority of the ring substituents in a *pseudo*-equatorial orientation.

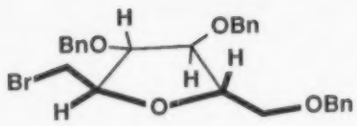
*For the analogous formation of a *cis*-fused lactone, see ref. 29.



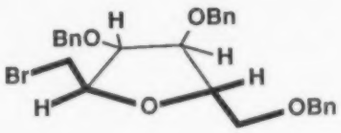
34



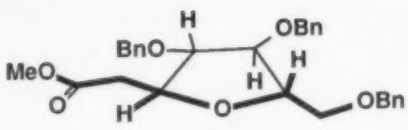
10



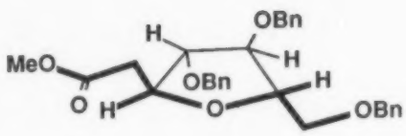
9a



9b



33a



33b

Fig. 1. Low-energy conformations for **9, 10, 33**, and **34** determined by MMP2 (L configurations shown).

TABLE I

ENERGIES, AND CALCULATED DIHEDRAL ANGLES AND VICINAL COUPLING CONSTANTS FOR EACH CONFORMATION OF **9, 10, 33**, AND **34**[a]

Structure	*MMP2 energy (kJ/mol)*	*Coupling constant (Hz)*[b] *and dihedral angle (degrees)*[c]		
		$J_{2,3}$ *or* $J_{3,4}$	$J_{3,4}$ *or* $J_{4,5}$	$J_{4,5}$ *or* $J_{5,6}$
9a	224.1	2.2 (110)	4.4 (131)	9.1 (153)
9b	221.3	3.4 (119)	6.2 (141)	10.0 (160)
10	219.2	3.4 (47)	0.8 (99)	4.0 (123)
33a	240.2	4.1 (123)	6.7 (144)	10.0 (161)
33b	247.3	0.7 (88)	0.9 (102)	5.0 (129)
34	238.1	3.6 (46)	0.8 (100)	4.1 (123)

[a]See Fig. 1. [b]Upper row, **9** and **10**; lower row, **33** and **34**. [c]Dihedral angle is given in parentheses.

The energy difference between the lowest-energy α and β conformations was only ~2.0 kJ/mol, with the β anomers being slightly preferred. This corresponds to only a 2:1 ratio of diastereomers at equilibrium, which is consistent with the lack of thermodynamic preference determined in the equilibration experiment on **33** and **34**.

In-depth n.m.r. experiments were conducted on mixtures of **9** and **10**, and **33** and **34**. ^{13}C-N.m.r. was used to determine the relative orientation of the β and α anomers[20,21]. Additionally, the carbon resonances for **9** and **10** were assigned by a ^{13}C–^{1}H heteronuclear, shift-correlated, two-dimensional n.m.r. experiment[32]. The ^{1}H-chemical-shift assignments were based on a series of ^{13}C(^{1}H)-selective decoupling experiments and by two-dimensional, ^{1}H–^{1}H homonuclear decoupled spectroscopy, along with standard shift-correlated (COSY) spectroscopy. Some of

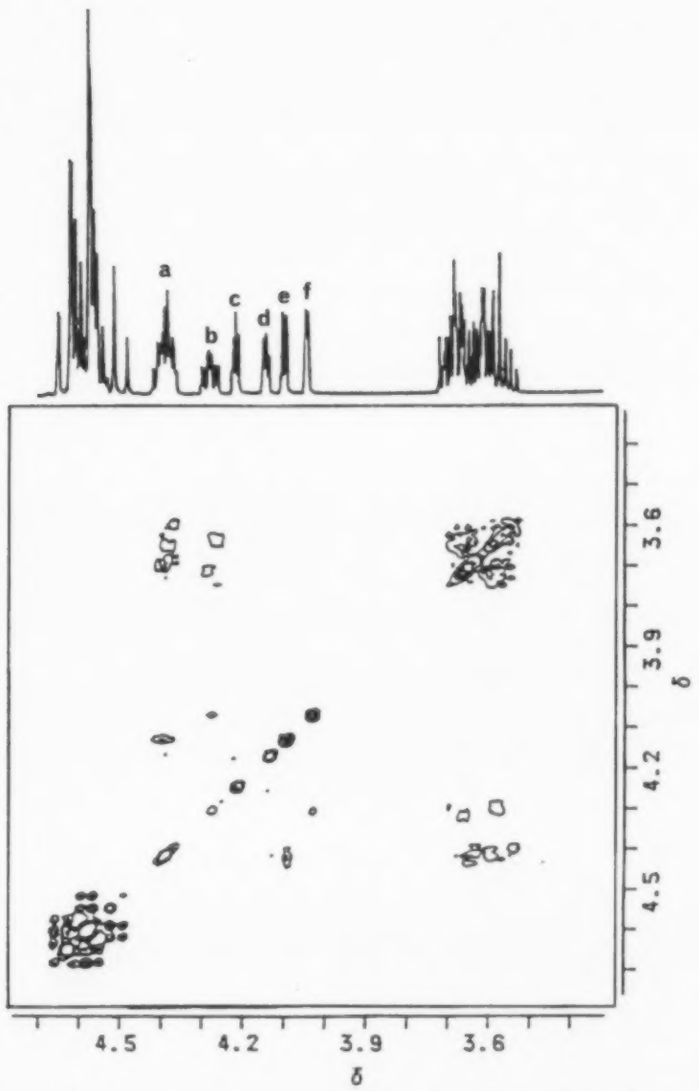


Fig. 2. A standard, one-dimensional spectrum (top) and a 2-D, *J*-correlated (COSY), ^{1}H-n.m.r. contour plot (bottom) of the aliphatic protons of **9** and **10** (9:11 mixture) obtained at 360 MHz. Assignments: a, H-2 and H-5 of **9** and H-2 of **10**; b, H-5 of **10**; c, H-3 of **9**; d, H-4 of **9**; e, H-3 of **10**; f, H-4 of **10**.

TABLE II

^{1}H-N.M.R. DATA FOR SELECTED PROTONS OF **9, 10** AND **33, 34**

Compound	*Chemical shifts (δ) and multiplicities*[a]							
9, 10 **33, 34**	*H-1a* *H-2a* *(dd)*	*H-1b* *H-2b* *(dd)*	*H-2* *H-3* *(ddd)*	*H-3* *H-4* *(dd)*	*H-4* *H-5* *(dd)*	*H-5* *H-6* *(ddd)*	*H-6a* *H-7a* *(dd)*	*H* *H* (
9	3.54[c]	3.48[c]	4.36	4.16	4.09	4.36	3.62[d]	3
10	3.61	3.54	4.37	4.04	3.98	4.23	3.63	3
33	3.50	3.56	4.22	4.02	3.90	4.48	2.65	2
34	3.47	3.56	4.06	3.92	3.97	4.44	2.74	2

[a]dd, Doublet of doublets; ddd, doublet of doublet of doublets; m, multiplet. [b]± because of overlapping resonances.

		Coupling constants (Hz)[b]								
H-6b *H-7b* *(dd)*		$J_{1a,1b}$ $J_{2a,2b}$	$J_{1a,2}$ $J_{2a,3}$	$J_{1b,2}$ $J_{2b,3}$	$J_{2,3}$ $J_{3,4}$	$J_{3,4}$ $J_{4,5}$	$J_{3,5}$ $J_{4,6}$	$J_{4,5}$ $J_{5,6}$	$J_{5,6a}$ $J_{6,7a}$	$J_{5,6b}$ $J_{6,7b}$
3.57[d]		[e]	[e]	[e]	2.8	2.2	0.5	3.3	[e]	[e]
3.52		[e]	5.9	8.0	3.7	0.9	0	2.5	6.0	6.8
2.63		12.0	6.1	6.1	3.2	[e]	[e]	[e]	[e]	[e]
2.74		12.0	6.2	6.2	3.1	[e]	[e]	[e]	[e]	[e]

t. [b]±0.1 Hz. [c,d]Assignments may be interchanged. [e]Values could not be determined

the coupling constants were undetermined because of overlap; nevertheless, most of the n.m.r. parameters could be determined. A 2-D, n.m.r. COSY experiment of a 9:11 mixture of **9** and **10** is plotted in Fig. 2. ^{1}H-N.m.r. data for these compounds are listed in Table II.

Several salient points can be discerned by inspection of the data in Table II. Comparison of the $J_{2,3}$ value of **9** and **10**, and the $J_{3,4}$ value for **33** and **34**, indicated only a very small difference (at most 1 Hz for **9** and **10**, and 0–0.3 Hz for **33** and **34**). Analysis of these chemical shifts or coupling constants could not have been used to assign relative stereochemistry. Because of small differences in n.m.r. chemical shifts and coupling constants, an attempt to assign the form of the oxolane ring based on these parameters may be fraught with error. Comparison of the coupling constants with those calculated from the MMP2 conformations, however, revealed a fairly close correlation (although the calculations represent gas-phase conditions and the n.m.r. experiments were conducted for deuteriochloroform solutions).

In conclusion, *C*-D-arabinofuranosyl compounds, selectively enriched in either the β or α anomer, were synthesized. The β configuration was obtained by electrophile-mediated cyclization of **8**, allowing for the preparation of the pure phosphonate anomer **4**. Wittig–Michael reactions of **7** with stabilized phosphoranes gave preponderantly the α anomer. The carbomethoxy derivatives **33** and **34** prepared in this manner, were transformed into carboxylates **5** and **6**, respectively. The biological activity of **4–6** was evaluated *in vitro*. For activation of phosphofructo-1-kinase, the concentrations for half-maximal activity were 31μM, >1mM, and >1mM, respectively. For inhibition of fructose-1,6-bisphosphatase, the IC_{50} values were 173μM, >1mM, and >1mM, respectively. In comparison, **2** activated phosphofructo-1-kinase with a concentration for half-maximal activity of 1μM, and inhibited fructose-1,6-bisphosphatase with an IC_{50} of 3.4μM. Thus, carboxylate isosteres **5** and **6** are inactive, whereas phosphonate **4** retains a significant portion of the activity of **2**. We are continuing to investigate electrophile-promoted cyclizations of **8**, and related compounds, to further define the diastereoselectivity.

EXPERIMENTAL

General methods. — Melting points were determined with a Thomas Hoover apparatus and are corrected. T.l.c. analysis was conducted on Whatman MK6F 200-μ silica gel plates. ^{1}H-N.m.r. spectra were recorded with either a Varian EM-360 (60 MHz), Varian EM-390 (90 MHz), or Bruker AM-360WB (360 MHz) spectrometer, as indicated. ^{13}C-N.m.r. spectra were recorded with a JEOL FX-60Q spectrometer operating at 15.0 MHz, or a Bruker AM-360WB spectrometer at 90.6 MHz where so noted. Where anomer ratios are reported for ^{1}H- and ^{13}C-n.m.r. experiments, integrations were obtained under quantitative conditions. Tetramethylsilane was used as an internal standard, except when D_2O was the solvent, in which case the spectra were referenced to external 1,4-dioxane. Elemental

analyses were performed primarily by Galbraith Laboratories (Knoxville, TN). Chemical-ionization mass spectra (c.i.m.s.) were recorded with a Finnigan 3300–6100 system with methane as the reagent gas, except where indicated otherwise. The starting material, 3,5-di-*O*-benzyl-D-arabinose[33] (**7**), was purchased from Pfanstiehl Laboratories (Waukegan, IL).

*3,4,6-Tri-*O*-benzyl-1,2-dideoxy-*D*-arabino-hex-1-enitol* (**8**). — To methyltriphenylphosphonium bromide (200 g, 0.56 mol) under Ar was added M lithium hexamethyldisilazanide (600 mL) in oxolane *via* a cannula. After being stirred for 30 min, the solution had a deep-red color and only a small amount of residual solid remained. Compound **7** (100 g, 0.24 mol), suspended in oxolane (30 mL), was added causing a precipitate to form ($Ph_3PCH_3^+ \cdot Br^-$). After 15 min, water was slowly added and the product was extracted into ether, washed with water (4 ×), dried ($MgSO_4$), filtered, and evaporated *in vacuo*. Purification by preparative l.c. (Waters Prep 500; silica gel; 3:22 ethylacetate–hexane) gave a yellow oil (67.8 g) that was homogeneous by t.l.c. (68%), $[\alpha]_D^{22}$ +4.2° (*c* 1.5, methanol); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 2.8 (d, *J* 5 Hz, OH), 3.6 (m, 2 H), 3.8–4.1 (m, 3 H), 4.4–4.7 (m, 6 H, CH_2Ph), 5.1–5.4 (m, 2 H), 5.6–6.1 (m, 1 H), and 7.2 (s, 15 H); the peak at δ 2.8 disappeared upon treatment with D_2O; $^{13}C(^1H)$-n.m.r. ($CDCl_3$): δ 70.2, 70.5, 70.8, 73.2, 73.9, 80.0, 80.4, 118.7, 127–129 (15 C), 135.0, and 138.0 (3 C).

Anal. Calc. for $C_{27}H_{30}O_4$: C, 77.48; H, 7.22. Found: C, 77.67; H, 7.40.

*2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-bromo-1-deoxy-*D*-mannitol* (**9**) *and 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-bromo-1-deoxy-*D*-glucitol* (**10**). — To a solution of **8** (1 g, 2.4 mmol) in dichloromethane (3 mL) at 0° was added *N*-bromosuccinimide (446 mg, 2.5 mmol). After 15 min, t.l.c. showed complete conversion to a faster-moving spot. Succinimide was filtered off and the solvent was removed to give a near quantitative yield of a mixture of **9** and **10**, contaminated by a little succinimide. Analytically pure material was obtained by chromatography of a small portion on silica gel (7:3 ethyl acetate–hexane). The ratio of epimers was determined by integration of the signals for the protons at C-3 and C-4 of **9** and **10**, and determined to be 11:89, respectively (see Table I for ^{1}H-n.m.r. data). $^{13}C(^1H)$-N.m.r. ($CDCl_3$; 90.6 MHz): δ 28.24 (C-1, **10**), 32.33 (C-1, **9**), 70.12 (C-6, **9** or **10**), 70.16 (C-6, **9** or **10**), 81.28 (C-2, **10**), 82.69 (C-2, **9**), 82.21 (C-3, **10**), 82.83 (C-5, **9**), 83.14 (C-4, **10**), 83.45 (C-5, **10**), 84.68 (C-4, **9**), 85.33 (C-3, **9**), 127.8 (9 C), 128.4 (6 C), 137.6 (2 C), and 138.0.

Anal. Calc. for $C_{27}H_{29}BrO_4$: C, 65.19; H, 5.88; Br, 16.06. Found: C, 65.10; H, 5.90; Br, 16.13.

*2,5-Anhydro-3,4-di-*O*-benzyl-1-deoxy-1-diphenoxyphosphinoyl-*D*-mannitol and 2,5-anhydro-3,4-di-*O*-benzyl-1-deoxy-1-diphenoxyphosphinoyl-*D*-glucitol* (**14**). — A solution of **9** and **10** (11:89 ratio; 1.0 g, 2.0 mmol) and ethyl diphenyl phosphite[17] (2.1 g, 8 mmol) was heated for 2 d at 160°. The product was purified by chromatography (dry silica gel column; 3:7 ethyl acetate–hexane) to give **13** (750 mg; of undetermined configuration; 57%); ^{1}H-n.m.r. ($CDCl_3$; 60 MHz): δ 2.55 (centered multiplet, apparent d of d, 2 H), 3.5–4.5 (m, 10 H), and 7.1 (m, 25 H);

c.i.m.s.: *m/z* 651 (MH^+). To a solution of **13** (8.3 g, 12.8 mmol) in dichloromethane (20 mL) was added iodotrimethylsilane (1.73 mL, 12.1 mmol) at 0° under N_2. The solution was allowed to warm to ambient temperature, and then stirred for 18 h. Water was added, the product was extracted into ether, and the solution washed with water twice, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by chromatography (Waters Prep-500 l.c.; 2:3 ethyl acetate–hexane) to give unreacted **13** (1.1 g), along with **14** (2.5 g), clear oil. The unreacted **13** that was recovered was a 17:3 mixture of the 2,5-anhydro-D-mannitol to the 2,5-anhydro-D-glucitol epimers. Thus, it appeared that iodotrimethylsilane had selectively deprotected the 2,5-anhydro-D-glucitol derivative; ^{1}H-n.m.r. ($CDCl_3$; 60 MHz): δ 2.52 (centered multiplet, apparent d of d, *J* 7, 19 Hz), 3.5–4.3 (m, 6 H), 4.5 (m, 4 H), and 7.1–7.3 (m, 10 H); c.i.m.s.: *m/z* 561 (MH^+).

2,5-Anhydro-3,4-di-O-benzyl-1-bromo-1-deoxy-D-mannitol diphenyl 6-phosphate and 2,5-anhydro-3,4-di-O-benzyl-1-bromo-1-deoxy-D-glucitol diphenyl 6-phosphate (**18**). — A 1% solution of H_2SO_4 in acetic anhydride (16 mL) was added dropwise to a solution of an 11:89 mixture of **9** and **10** in acetic anhydride (70 mL). The mixture was stirred for 1 h, cold water was added, and the product was extracted into dichloromethane (2 × 100 mL). The combined organic extracts were washed with 5% $NaHCO_3$, NaCl solution, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography (Waters Prep 500 l.c.; 1:6 ethyl acetate–hexane) to give **16** (13.6 g, 86%), of undetermined configuration; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 1.9 (s, 3 H), 3.5 (m, 2 H), 3.6–4.5 (m, 10 H), and 7.2 (m, 10 H). To a mixture of **16** (13.6 g) in methanol (150 mL) was added 18% aq. NaOH (26 mL) at 35°. After being stirred for 5 min, the solution was concentrated and the product was extracted into dichloromethane, washed with water (2 × 30 mL), NaCl solution, dried ($MgSO_4$), and evaporated to give **17** (10.9 g, 92%) as a colorless syrup; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 2.1 (t, 1 H), 3.4–3.9 (m, 4 H), 3.95–4.35 (m, 5 H), 4.4–4.6 (m, 4 H), and 7.1–7.3 (m, 10 H). To a cooled solution of **17** (10.7 g, 26 mmol) in pyridine (50 mL) was added dropwise a solution of diphenyl phosphorochloridate (7.7 g, 29 mmol) in dichloromethane (5 mL) at 5°. The mixture was stirred for 45 min at ambient temperature, treated with water, and extracted into dichloromethane. The combined organic extracts were washed with M HCl and an NaCl solution, then dried ($MgSO_4$), and evaporated. The residue was purified by chromatography (Waters Prep 500 l.c.; 1:3 ethyl acetate–hexane) to give **18** (11.3 g, 67%), colorless syrup; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 3.9–4.1 (m, 2 H), 4.2–4.6 (m, 7 H), and 7.1–7.6 (m, 2 H).

Anal. Calc. for $C_{32}H_{32}BrOP$: C, 60.10; H, 5.10. Found: C, 60.29; H, 5.10.

2,5-Anhydro-3,4-O-benzyl-1-deoxy-1-diphenoxyphosphinoyl-D-glucitol diphenyl 6-phosphate (**15**). — *From* **14**. A solution of **14** (3.3 g, 5.9 mmol) in pyridine (30 mL) was treated with diphenyl phosphorochloridate (1.22 mL, 6.2 mmol) at 0°. The solution was allowed to warm to ambient temperature and stirred overnight. The product was extracted into ether, washed with water thrice, dried ($MgSO_4$), filtered, and concentrated. Azeotropic evaporation of the remaining pyridine (with

toluene), treatment with activated charcoal (in ether), and crystallization from ether–hexane gave **15** (3.8 g, 81%), m.p. 72–73.5°; $[\alpha]_D^{23}$ +16.7° (*c* 1.5, methanol); ^{1}H-n.m.r. (360 MHz, $CDCl_3$): δ 2.55 (centered multiplet, apparent d of d of d, 2 H, *J* 2, 6, 16 Hz), 3.96 (d, 1 H, *J* ~1 Hz), 4.02 (d, 1 H, *J* 3.4 Hz), 4.35–4.5 (m, 4 H), 4.6 (m, 6 H), and 7.1–7.35 (m, 30 H); ^{13}C(^{1}H)-n.m.r. (90.6 MHz, $CDCl_3$): δ 26.15 (d, $J_{C,P}$ 142.0 Hz), 68.15 (d, $J_{C,P}$ 6.2 Hz), 71.74, 72.02, 76.4, 82.00 (d, $J_{C,P}$ 8.5 Hz), 82.55 (d, $J_{C,P}$ 5.8 Hz), 82.98, 120.05 (d, 8 C, $J_{C,P}$ 2.7 Hz), 120.62 (d, 8 C, $J_{C,P}$ 2.4 Hz), 125–130 (14 C, arom.), 137.39 (d, 2 C, $J_{C,P}$ 3.5 Hz), and 150.2–150.5 (4 C).

Anal. Calc. for $C_{44}H_{42}O_{10}P_2$: C, 66.66; H, 5.34; P, 7.81. Found: C, 66.38; H, 5.44; P, 7.89.

From **18**. A suspension of **18** (10.8 g, 17 mmol) and ethyl diphenyl phosphite (20 g, 76 mmol) was stirred for 16 h at 178°. The product was purified by chromatography (Waters Prep-500 l.c.; 1:2 ethyl acetate–hexane) to give a waxy solid (5.2 g, 39%), which was recrystallized from ether–hexane, m.p. 72–73°.

*2,5-Anhydro-3,4-di-*O*-benzyl-1-deoxy-1-dimethoxyphosphinoyl-*D*-glucitol dimethyl 6-phosphate* (**19**). — A solution of **15** (1.98 g, 2.5 mmol) in methanol (70 mL) was treated with CsF (1.5 g, 10 mmol) at reflux for 15 h, and then evaporated. The residue was purified on silica gel (97:3 ethyl acetate–methanol) to give a yellow oil (**19**) that was homogeneous by t.l.c. (887 mg, 65%). Refluxing **15** in methanol for 15 h in the absence of fluoride resulted in no reaction. Substitution of tetrabutylammonium fluoride (commercial M solution in oxolane) for CsF gave a comparable yield of **19** (63%); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 2.18 (dd, 2 H, $J_{H,P}$ 7, 19 Hz), 3.5 (d, 12 H, $J_{H,P}$ 11 Hz), 3.7–4.1 (m, 6 H), 4.3–4.4 (m, 4 H), and 7.2 (s, 10 H); ^{13}C(^{1}H)-n.m.r. ($CDCl_3$): δ 24.8 (d, $J_{C,P}$ 141.6 Hz), 52.6 (d, $J_{C,P}$ 4.9 Hz, 2 C), 54.3 (d, $J_{C,P}$ 5.9 Hz, 2 C), 67.1 (d, $J_{C,P}$ 5.9 Hz), 70–73 (2 C), 76.4, 81.9, 82.4, 82.8, 127–130 (10 C), and 137.4 (2 C); c.i.m.s.: *m/z* 545 (MH^+).

Anal. Calc. for $C_{24}H_{34}O_{10}P_2 \cdot 0.25\ H_2O$: C, 52.51; H, 6.33; P, 11.28; H_2O, 0.82. Found: C, 52.71; H, 6.41; P, 11.23; H_2O, 1.16.

*Dilithium 2,5-anhydro-1-deoxy-1-phosphono-*D*-glucitol 6-phosphate hydrate* (**4**). — A stirred solution of **15** (1.0 g) in oxolane (5 mL) was treated with 10% tetrabutylammonium hydroxide in oxolane (10 mL). After 24 h, the solution was acidified to a pH of ~2 with M HCl, and the product was extracted into chloroform (6 vol.). The solution was dried ($MgSO_4$), filtered, and evaporated to give a clear oil (900 mg); ^{1}H-n.m.r. (90 MHz) indicated the absence of any tetrabutylammonium groups; c.i.m.s.: *m/z* 641 (MH^+). This material was dissolved in 3:7 2,2-dimethylpropanol–water (30 mL) and shaken with 10% Pd–C (2.05 g) under H_2 (0.34 MPa). After 24 h, additional water (10 mL) was added along with PtO_2 (2.5 g). The solution was shaken under H_2 (0.34 MPa) for another day, and then filtered; the catalyst was washed with water (40 mL). The filtrate was partially concentrated (to ~20 mL) and then lyophilized. The resultant white solid was redissolved in water (2 mL) and treated with M NaOH until pH 5.0 was reached. Treatment with methanol caused a flocculent precipitate to form (168 mg, 34%), m.p. >250° (dec); $[\alpha]_D^{20}$ +24.5° (*c* 2.1, water); ^{1}H-n.m.r. (360 MHz, D_2O): δ 1.73 (cen-

tered multiplet, apparent t, J ~7 Hz, PCH_a), 1.78 (centered multiplet, apparent t, J ~7 Hz, PCH_b), 3.6–3.78 (m, 3 H), 3.82 (d, J 2.4 Hz), 3.87 (d, J 2.5 Hz), and 3.9–4.06 (m, 1 H); $^{13}C(^1H)$-n.m.r. (D_2O): δ 27.9 (d, $J_{C,P}$ 130.9 Hz), 64.8 (d, $J_{C,P}$ 4.9 Hz), 77.9 (d, $J_{C,P}$ 5.8 Hz), 78.1, 78.5, and 83.6 (d, $J_{C,P}$ 7.8 Hz).

Anal. Calc. for $C_6H_{12}Na_2O_{10}P_2 \cdot 0.1\ CH_3OH \cdot 1.2\ H_2O$: C, 19.44; H, 3.96; H_2O, 5.74. Found: C, 19.43; H, 4.35; H_2O, 5.43.

The analyses for P and Na deviated from the calculated values. Considering the amorphous, hygroscopic nature of the compound, the structural assignment was based largely on the n.m.r. spectra, which had no unassigned resonances.

*2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-diethoxyphosphinoyl-*D*-glucitol* (**22**) *and 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-diethoxyphosphinoyl-*D*-mannitol* (**23**). — To a solution of **7** (420 mg, 1 mmol) and **21** (516 mg, 2 mmol) in oxolane (1 mL) was added M lithium bis(trimethylsilyl)amide in oxolane (1.1 mL). After stirring for 5 h at ambient temperature, little reaction was observed by t.l.c., so the solution was heated for 4 h at 40–50°. Additional molar equiv. of base and **21** were added (1.0 mL of M lithium bis(trimethylsilyl)amide in oxolane and 260 mg of **21**), and the solution was stirred for 4 d at ambient temperature. The solution was treated with water, and the product was extracted into dichloromethane, washed with water (2 ×), dried ($MgSO_4$), filtered, and concentrated. The residue was purified on silica gel (3:2 ethyl acetate–chloroform) to give **22** and **23** (290 mg, 50%); ^1H-n.m.r. (90 MHz, $CDCl_3$): δ 1.2 (m, 6 H), 2.2 (apparent d of d, J 7.18 Hz), 3.5 (m, 2 H), 3.7–4.3 (m, 10 H), 4.3–4.5 (m, 6 H), and 7.2 (s, 15 H); $^{13}C(^1H)$-n.m.r. ($CDCl_3$): δ 16.4 (d, 2 C, $J_{C,P}$ 5.9 Hz), 25.9 (d, 0.37 C, $J_{C,P}$ 141.6 Hz), 30.2 (d, 0.63 C, $J_{C,P}$ 137.7 Hz), 61–62 (m, 2 C), 70–74.5 (m, 4 C), 75–88 (4 C), 127–130 (m, 15 C), 137.9, 138.1, and 138.3; c.i.m.s. (NH_3): m/z 555 (MH^+, 90% of base peak), and 556 ($MH^+ + 1$, 30% of base peak).

*2,3,5-Tri-*O*-benzyl-4-*O*-(*tert*-butyldimethylsilyl)-*D*-arabinose ethylene dithioacetal* (**29**). — A mixture of **7** (60 g, 0.14 mol), 1,3-propanedithiol (55.6 g, 0.52 mol), and methanesulfonic acid (15 mL) in benzene (500 mL) was stirred for 2 h. The solution was then washed with 3M NaOH and NaCl solution, dried (Na_2SO_4), filtered, and evaporated to give a pale-yellow syrup, **28**, pure by t.l.c. (72.3 g, 99%); c.i.m.s.: m/z 511 ($M + 1$). A mixture of crude **28** (8.05 g, 0.016 mol), *tert*-butylchlorodimethylsilane (6.75 g, 0.045 mol), and imidazole (8.19 g, 0.12 mol) in *N,N*-dimethylformamide (30 mL) was stirred under N_2 for 4 h at 60°. The mixture was poured into water and extracted into dichloromethane (2 × 50 mL). The combined organic layers were washed once with NaCl solution, dried (Na_2SO_4), filtered, and concentrated to give **29** as a colorless syrup (8.9 g, 89%), pure by t.l.c.; ^1H-n.m.r. (90 MHz, $CDCl_3$): δ 0.2 (s, 6 H), 0.9 (s, 9 H), 1.8–2.2 (m, 3 H), 2.9 (m, 4 H), 4.5–4.8 (m, 6 H), and 7.3 (m, 15 H); c.i.m.s.: m/z 625 ($M + 1$).

*2,3,5-Tri-*O*-benzyl-4-*O*-(tert-butyldimethylsilyl)-aldehydo-*D*-arabinose* (**30**). — A solution of dithiane **29** (1.6 g, 2.6 mmol) in acetonitrile (17 mL) was added dropwise to a solution of *N*-bromosuccinimide (3.6 g, 20 mmol) in 80% aqueous acetonitrile (35 mL) at −10°. After being stirred for 5 min, the mixture was poured

into saturated aqueous $Na_2S_2O_3$ and extracted twice with ether (2 × 25 mL). The combined extracts were washed with water, dried (Na_2SO_4), filtered, and concentrated to give **30** as a pale-yellow syrup (near quantitative yield), pure by t.l.c.; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 0.0 (m, 6 H), 0.8 (m, 9 H), 3.2–4.1 (m, 5 H), 4.3–4.6 (m, 6 H), and 7.1 (m, 15 H).

A mixture of the *aldehydo* sugar **30** (0.37 g, 0.69 mmol) and phosphorane **20** (1.2 g, 2.4 mmol) in benzene (5 mL) was refluxed under N_2 for 18 h. The solution was evaporated to a syrup which was purified by chromatography on preparative t.l.c. (1:1 ethyl acetate–hexane) to give **26** (0.33 g, 31%) pale-yellow syrup, pure by t.l.c.; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 0.0 (s, 6 H), 0.8 (s, 9 H), 3.3–4.25 (m, 5 H), 4.3–4.6 (m, 6 H), 6.1–6.8 (m, 2 H), and 7–7.4 (m, 15 H); ^{1}H-n.m.r. (360 MHz, $CDCl_3$) revealed a similar pattern in the vinylic region [δ peak centered at 6.25 (H-1), ~7.1 (H-2)] to that observed for **27**, supporting the *E* stereochemical assignment; the signal for H-2 was obscured under the aromatic proton signals; c.i.m.s.: *m/z* 765 (M + 1).

A M solution of lithium bis(trimethylsilyl)amide in oxolane (2.7 mL) was added to a solution of tetraethyl methylenediphosphonate (**21**; 0.7 g, 2.4 mmol) in oxolane (5 mL) under N_2. A solution of the *aldehydo* sugar **30** (0.48 g, 0.88 mmol) in oxolane (5 mL) was added, and it was stirred for 18 h at ambient temperature, poured into water, and extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were washed once with an NaCl solution, dried (Na_2SO_4), filtered, and concentrated to give a pale-yellow syrup, which was purified by chromatography on preparative t.l.c. plates (1:1 ethyl acetate–hexane) to give pure **27**, (0.18 g, 31%), oil, pure by t.l.c.; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 0.1 (s, 6 H), 0.9 (s, 9 H), 1.3 (t, 6 H), 3.4–3.8 (m, 3 H), 4.0 (t, 4 H), 4.1–4.3 (m, 2 H), 4.3–4.6 (m, 6 H), 5.6–6.1 (m, 1 H), 6.3–6.8 (m, 1 H), and 7.3 (m, 15 H); ^{1}H-n.m.r. (360 MHz, $CDCl_3$; vinylic region): δ 6.01 (ddd, $J_{H,P}$ 21.1, $J_{1,2}$ 17.3, $J_{1,3}$ 1.4 Hz, H-1), and 6.82 (ddd, $J_{H,P}$ 22.5, $J_{1,2}$ 17.3, $J_{2,3}$ 5.5 Hz, H-2); this supports the *E* configurational assignment for **27**.

A mixture of **27** (65 mg, 97 mmol) in oxolane (2 mL) was treated with M tetrabutylammonium fluoride in oxolane (15 mL), and stirred under N_2 for 2 h. The solution was then poured into 3M NaOH and extracted into ethyl acetate (2 × 5 mL). The combined organic extracts were washed with NaCl solution, dried (Na_2SO_4), filtered, and concentrated to a syrup which was purified by chromatography on a preparative t.l.c. plate (4:1 ethyl acetate–hexane) to give **22** and **23** (13.3 mg, 25%), whose ^{1}H-n.m.r. spectrum was identical with that described above.

*Mixture of methyl 3,6-anhydro-4,5,7-tri-*O*-benzyl-2-deoxy-*D-glycero-D-galacto-*heptonate* (**33**) *and methyl 3,6-anhydro-4,5,7-tri-*O*-benzyl-2-deoxy-*D-glycero-D-gulo-*heptonate* (**34**). — A mixture of **7** (20 g, 48 mmol) and **31** (26 g, 77 mmol) was refluxed in acetonitrile (200 mL) for 24 h. The solution was evaporated and the residue purified by chromatography (dry silica gel column; 1:6 ethyl acetate–hexane) to give a mixture of **33** and **34** (20 g, 88%), colorless syrup; $[\alpha]_D^{23}$ +21.4° (*c* 0.52, methanol); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 2.6 (d, 2 H), 3.5 (m, 2

H), 3.7 (s, 3 H), 3.75–4.4 (m, 4 H), 4.5 (m, 6 H), and 7.2 (m, 15 H); $^{13}C(^{1}H)$-n.m.r. ($CDCl_3$): δ 34.1 (CH_2CO_2, **34**, ~0.11 C), 38.1 (CH_2CO_2, **33**, ~0.89 C), 51.6, 82.1, 82.9, 85.0, 86.6, 127–129 (15 C, arom.), 137.7 (3 C), 138.0, and 171.0.

Anal. Calc. for $C_{29}H_{32}O_6$: C, 73.09; H, 6.77. Found: C, 72.87; H, 6.71.

Equilibration of **33** *and* **34**. — A solution of a 5:1 mixture of **33** and **34** (125 mg) in methanol (0.5 mL) was treated with 25% sodium methoxide in methanol[20,21] (28 μL). After 18 h, water was added, the product was extracted into ether, and the extract washed with water, dried ($MgSO_4$), filtered, and evaporated; ^{13}C-n.m.r. showed a 1:1 ratio of **33** and **34** by inspection of their respective C-2 resonances at δ 38.0 and 34.1, respectively. Similar treatment of **33** and **34** for 6 d also resulted in a 1:1 ratio.

*Mixture of 3,6-anhydro-4,5,7-tri-*O*-benzyl-2-deoxy-*D-glycero-D-galacto-*heptononitrile* (**35**) *and 3,6-anhydro-4,5,7-tri-*O*-benzyl-2-deoxy-*D-glycero-D-gulo-*heptononitrile* (**36**). — A suspension of **7** (6.0 g, 14.3 mmol) and **32** (ref. 27; 5.0 g, 16.7 mmol) in acetonitrile (80 mL) was heated under reflux for 2 d. The yellow solution was cooled and filtered, and the filtrate concentrated. The residue was chromatographed (flash chromatography on silica gel; 3:7 ethyl acetate–hexane) to give a 67:33 mixture of **35** and **36** (5.51 g, 87%); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 2.6 (centered multiplet, apparent t, 2 H), 3.52 (d, 2 H, *J* 5 Hz), 3.9–4.45 (m, 4 H), 4.5 (s, 6 H), and 7.3 (s, 15 H); $^{13}C(^{1}H)$-n.m.r. ($CDCl_3$): δ 18.3 (C-2, **36**, 0.32 C), 22.0 (C-2, **35**, 0.68 C), 68–74 (4 C), 78–86 (4 C), 116.9, 127–129 (15 C), 137.5, 137.6, and 138.1.

Anal. Calc. for $C_{28}H_{29}NO_4$: C, 75.83; H, 6.59; N, 3.16. Found: C, 75.57; H, 6.63; N, 3.08.

*Methyl 3,6-anhydro-2-deoxy-*D-glycero-D-galacto-*heptonate* (**37**) *and 3,6-anhydro-2-deoxy-*D-glycero-D-gulo-*heptono-1,4-lactone* (**39**). — A 9:1 mixture of **33** and **34** (24 g, 50 mmol) in ethanol (600 mL) was shaken with 10% Pd–C (7.9 g) under 0.34 MPa of H_2 for 18 h. The solution was filtered and the filtrate concentrated. The residue was chromatographed (Waters Prep 500 l.c.; 6:1 ethyl acetate–hexane) to give **37** (5.3 g, 51%) and **39** (1.3 g, 15%), colorless syrups, R_F (6:1 ethyl acetate–hexane) 0.21 (**37**) and 0.25 (**39**); ^{1}H-n.m.r. (90 MHz, D_2O) for **37**: δ 2.6–2.8 (m, 2 H), 3.5–3.7 (m, 2 H), 3.7 (s, 3 H), and 3.8–4.4 (m, 4 H); for **39**: δ 2.9–3.1 (m, 2 H), 3.5–3.85 (m, 2 H), 3.9–4.5 (m, 2 H), and 5.0–5.2 (m, 2 H, H-3,4); c.i.m.s. (**37**): *m/z* 175 (MH^+).

*Trisodium 3,6-anhydro-2-deoxy-*D-glycero-D-galacto-*heptonate 7-phosphate tetrahydrate* (**5**). — A solution of diphenyl phosphorochloridate (5.9 g, 22 mmol) in toluene (10 mL) was added dropwise to a solution of **37** (4.6 g, 22 mmol) in pyridine (30 mL) at −30°. The mixture was stirred for 4.5 h at 0°, treated with cold water, and extracted into dichloromethane (2 × 50 mL). The combined organic extracts were washed with water and NaCl solution, then dried (Na_2SO_4), filtered, and concentrated. The residue was purified on a dry silica gel column (4:1 ethyl acetate–hexane) to give **38** (4.98 g, 52%), colorless syrup; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 2.5 (d, 2 H), 3.6 (s, 3 H), 3.9–4.4 (m, 8 H), and 7.2 (m, 10 H); $^{13}C(^{1}H)$-n.m.r.

($CDCl_3$): δ 38.1 (CH_2CO_2), 51.8, 68.3 ($J_{C,P}$ 5.9 Hz), 77.8, 80.6, 80.9, 81.8, 120.2 (4 C), 125.5 (2 C), 129.8 (4 C), and 150.2 (d, 2 C, $J_{C,P}$ 6.8 Hz); c.i.m.s.: *m/z* 439 (MH^+).

A solution of **38** (4.85 g, 11 mmol) in methanol (100 mL) was shaken with PtO_2 (2.0 g) under H_2 (0.34 MPa) for 1.5 h. The suspension was filtered, and the filtrate concentrated and treated with aq. NaOH (1.27 g in 20 mL of water). After 4 h, the solution was lyophilized to furnish **5** (3.5 g, 76%), white foam, $[\alpha]_D^{25}$ +17° (*c* 1.5, water); ^{1}H-n.m.r. (90 MHz, D_2O): δ 2.6 (d, 2 H), and 3.8–4.6 (m, 6 H); $^{13}C(^1H)$-n.m.r. (D_2O): δ 41.1 (CH_2CO_2), 63.7 (d, $J_{C,P}$ 3.9 Hz), 76.8, 79.9, 80.1, 81.5 (d, $J_{C,P}$ 7.9 Hz), and 179.2.

Anal. Calc. for $C_7H_{10}Na_3O_9P \cdot 3.8\ H_2O$: C, 20.68; H, 4.36; Na, 16.96; P, 7.61; H_2O, 16.83. Found: C, 20.99; H, 4.42; Na, 16.59; P, 7.90; H_2O, 15.80.

Trisodium 3,6-anhydro-2-deoxy-D-glycero-D-gulo-*heptonate 7-phosphate tetrahydrate* (**6**). — A solution of diphenyl phosphorochloridate (1.69 g, 6.3 mmol) in toluene (2 mL) was added dropwise to a solution of **39** (1.0 g, 5.7 mmol) in pyridine (10 mL) at −30°, followed by addition of 4-(dimethylamino)pyridine (50 mg). The mixture was stirred for 5 h at 0°, treated with cold water, and the product extracted into dichloromethane. The organic layer was washed with water and an NaCl solution, then dried (Na_2SO_4), filtered, and concentrated. The beige residue was chromatographed (dry column of silica gel; 4:1 ethyl acetate–hexane) to afford **40** (0.60 g, 28%) colorless syrup; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 2.8 (m, 2 H), 3.8–4.6 (m, 5 H), 4.8 (m, 2 H, H-3,4), and 7.1–7.5 (m, 10 H).

A solution of **40** (0.6 g) in methanol (20 mL) was shaken with PtO_2 (0.32 g) under H_2 (0.34 MPa) for 2.5 h. The solution was filtered and the filtrate concentrated. The residue was treated with aq. NaOH (0.15 g in 5 mL of water) for 1.5 h. The solution was lyophilized to give **6** (0.41 g, 18%, from **39**), crisp foam, $[\alpha]_D^{25}$ +13.6° (*c* 0.90, water); ^{1}H-n.m.r. (90 MHz, D_2O): δ 2.6 (d, 2 H) and 3.8–4.6 (m, 6 H); $^{13}C(^1H)$-n.m.r. (D_2O): 36.6 (CH_2CO_2), 63.9 (d, *J* 4.9 Hz), 77.6, 78.8, 78.9, 84.0 (d, $J_{C,P}$ 8.8 Hz), and 179.2.

Anal. Calc. for $C_7H_{10}Na_3O_9P \cdot 3.8\ H_2O$: C, 20.68; H, 4.36; Na, 16.96; P, 7.61; H_2O, 16.33. Found: c, 20.99; H, 4.42; Na, 16.59; P, 7.90; H_2O, 15.80.

2-D N.m.r. experiments[32]. — The 2-D n.m.r. spectra were recorded with a Bruker AM-360WB instrument using standard Bruker software. The COSY-2D, ^{1}H-n.m.r. experiments were performed in a 5-mm probe, at a concentration of 15 mg/0.5 mL, using a 90° pulse, 6.9 μs, a 3.03-s recycle time, and 16 acquisitions per data set. For **9** and **10**, a spectral width of 1700.0 Hz in F_1 and F_2 was used with a 512W × 256W transform, and for **33** and **34**, a spectral width of 1501.5 Hz in F_1 and F_2 with a 2K × 1K transform. The data were processed with a sine-bell, window function, and diagonally symmetrized.

The ^{13}C–^1H, COSY-2D n.m.r. experiment was performed on a 150 mg/2.0 mL solution of **9** and **10** in a 10-mm probe using a 90° pulse, 16 μs for ^{13}C, and a 90° pulse, 43 μs for ^1H on the decoupler coil of a VPS broadband-probe head. A 3.06-s recycle time with 64 acquisitions per data set and a spectral width of 8928.6

Hz in F_2 and 1700.6 Hz in F_1 were utilized. A 1K × 512W transform and a sine-bell window function was used in processing.

EFF calculations. — Energy minimizations were performed with the MMP2 force field[31]. In order to insure against obtaining false minima due to unfavorable side-chain rotamers, the full spectrum of rotations (360° in 10° increments) was separately examined for each of the following bonds (for **9, 10** and **33, 34**, respectively): C-5/6, C-6/7; C-6/7, O; C-4/5, O; C-3/4, O; all of the $PhCH_2$, O bonds; and the two single bonds to C-1 of **33, 34**. After placing each of the key bonds in its locally minimized form, the molecule was then subjected to a full structure–energy minimization procedure.

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SYNTHESIS OF (2-DEOXY-α-D-GLYC-2-ENOPYRANOSYL)ARENES BY STEREOSPECIFIC CONJUGATE-ADDITION OF ORGANOCOPPER REAGENTS TO PERACETYLATED HEX-1-ENOPYRAN-3-ULOSES*

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ABSTRACT

The reaction of peracetylated 1,5-anhydro-2-deoxyhex-1-eno-3-uloses with higher-order cyanoorganocuprate in oxolane at low temperature in the presence of acetic anhydride afforded the corresponding glycosylarenes in good yields. A complete stereocontrol could be achieved, leading to the α-D anomer without epimerization at C-4. The configuration of the new products was established by spectroscopic methods and transformation into the crystalline parent oximes, the conformation of which is discussed in terms of stereoelectronic effects.

INTRODUCTION

Our laboratory is interested in the synthesis of glycosylarenes with a possible extension to complex aromatic components, including anthraquinone derivatives, and to heterocycles as an entry to *C*-nucleosides, some of which exhibit interesting biological activities[3]. Our efforts are particularly directed toward the study of methods affording new access to 2-deoxyglycosylarenes. Such subunits are often present in natural compounds and, in some cases, OH-6 may be missing and OH-3 be replaced by an amino group[4]. Generally *C*-glycosyl compounds have been prepared by nucleophilic attack on a suitably activated anomeric carbon of protected sugar derivatives (Scheme 1)[5].

These methods could be applied to 2-deoxyglycosyl derivatives, but we thought it would be of interest to explore the conjugate addition of organocopper reagents to protected hex-1-enopyran-3-uloses as an alternative route to this class of compounds, since the stereochemical outcome could be different. The copper-mediated conjugate addition to α,β-enones is well documented[6,7] and plays an in-

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Scheme 1.

creasingly important role in C–C bond formation. This reaction was often used to prepare branched-chain sugars[8] but, to the best of our knowledge, only two attempts were made with protected hex-1-enopyran-3-uloses to prepare *C*-glycosyl compounds[9,10]. Unlike these predecessors who used permanent protective groups, we took advantage of the relative inertness of organocopper reagents towards ester groups and hence acetate was used as a temporary protective group.

RESULTS AND DISCUSSION

The recently available[11] 4,6-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*erythro*- (**1**) and -D-*threo*-hex-1-eno-3-ulose (**2**) were treated under various conditions with different combinations of organocopper reagents in order to examine the influence of several factors (solvent, nature and quantity of reagent, temperature, etc.) (see Table I).

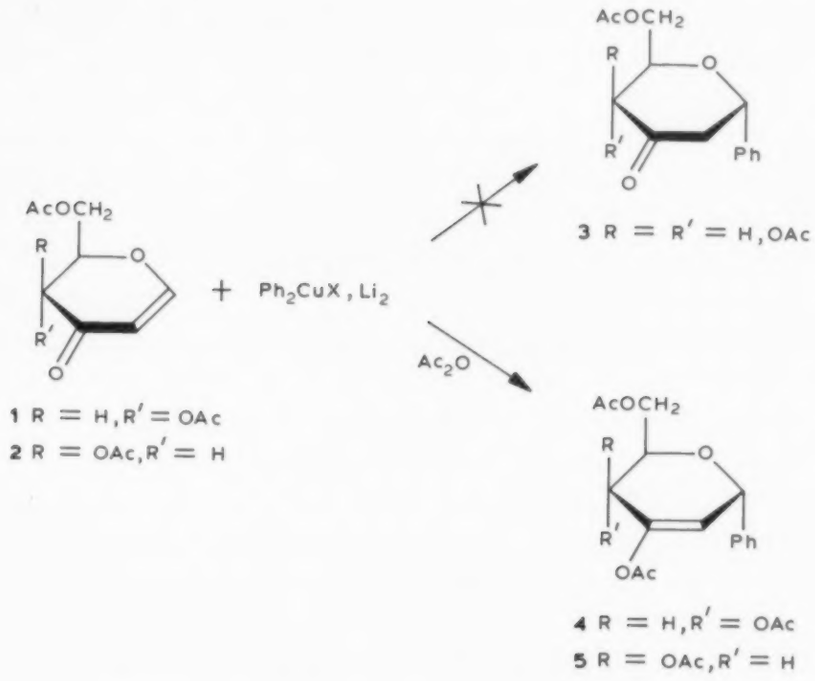
Although Goodwin *et al.*[10] obtained satisfactory yields of 3-keto-*C*-glycosyl compounds when treating alkyl heterocuprates in the presence of ether protective

TABLE I

REACTION OF ORGANOCOPPER REAGENTS WITH ENONES **1** AND **2**

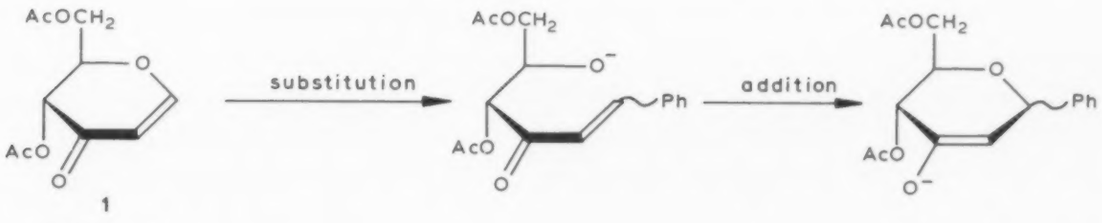
Exp.	*Enone (mmol)*	*Lithium salts (mmol)*	*Ac_2O*[a]	*$Ph_2CuCNLi_2$ (eq.)*	*Conditions*	*Yield of products (%)*[b]	
						4	**5**
1	**1** (0.5)	0.026	af.	1.05	−50→0°, 3 h at 0°, and 12 h at 20°	28[c](93)	2(7)
2	**1** (0.5)	0.05	af.	2	−50→0° and 2 h at 0°	75[d]	
3	**1** (1.5)	present[e]	af.	2	−50→0° and 2 h at 0°	74(96)	3(4)
4	**1** (3)	0.30	af.	2	−50→−25°	75(98.7)	1(1.3)
5	**1** (3)	0.30	tog.	2	−50→−25°	87(100)	0(0)
6	**2** (3)	0.30	tog.	2	−50→−25°	3(3.5)	83(96.5)

[a]Ac_2O (2 eq.) was added after (af.) or together with (tog.) the enone. [b]Yield of isolated product after flash chromatography. The proportions of **4** and **5** were also measured by g.l.c. analysis of the crude mixture. Relative proportions in parentheses. [c]Unreacted **1** (41%) was recovered. [d]Mixture containing 95% of **4** and 5% of **5** (g.l.c. analysis). [e]The percentage of lithium salts was not given in the solution sold by Fluka.



groups, no 3-keto-*C*-glycosylbenzene **3** resulting from a 1,4-addition could be isolated. Whatever the phenylcopper reagent was, t.l.c. showed the disappearance of the starting enone and essentially the presence of polar compounds, likely to be formed by reaction of the intermediate enolate with ester groups. The reactive enolate was quenched with acetic anhydride and the enol ester **4** was obtained in good yield, but an excess of organocopper was necessary to achieve completion of the reaction (Exps. 2 and 3). With a stoichiometric amount of organocopper (Exp. 1), 41% of starting enone was recovered, indicating that some organocopper reagent was consumed by a reaction with the trapping reagent or with the primary acetate group, or both[12].

The course of the reaction of organocopper reagents with 3-alkoxy-enones is not as clear as with simple enones. It has been observed that substitution of the 3-alkoxy group by the organometal could occur with such substrates[13]. In the case of enone **1**, opening of the pyranose ring would result from such a substitution (Scheme 2).

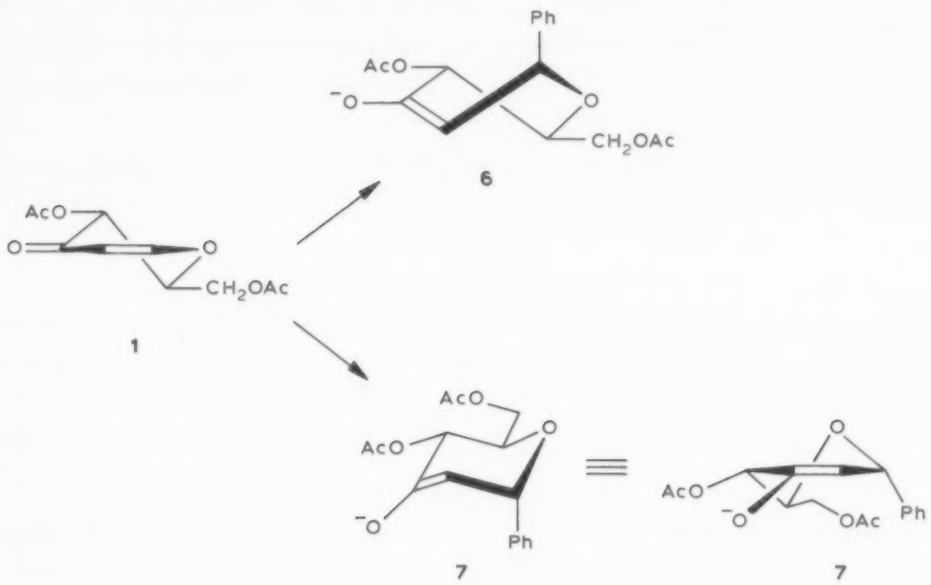


Scheme 2.

It is doubtful whether ring closure by a 1,4-nucleophilic addition could lead to

only one anomer. Moreover, when acetic anhydride was introduced together with the enone, the open structure would have been isolated, at least in small proportion. This substitution–addition sequence could be responsible for the lack of stereoselectivity observed by Yunker *et al.*[9] when treating 1,5-anhydro-4,6-*O*-benzylidene-2-deoxy-D-*erythro*-hex-1-en-3-ulose with dimethylcopperlithium, and by Paulsen and Bünsch[14] when treating the same enone with 2-lithio-1,3-dithiolane-2-carboxylate. The inertia of this rigid bicyclic enone and of the parent alcohols towards addition was also observed in our laboratory[15].

Under the conditions described herein, the reaction was stereospecific (no extra peak attribuable to the β anomer* could be detected by g.l.c. of the crude material), indicating that the flexibility of enone **1** allowed the direct addition of the organocopper compound in the usual manner. Considering the preferred conformation of enone **1**, as deduced from ^{1}H-n.m.r. data[11], it is suggested that an axial attack by the nucleophile with stereocontrol on the β face would lead to an enolate **6** having a boat-like conformation whereas that on the α face would give the enolate **7** having a chair-like conformation. The second process would, therefore, be favored as suggested by Toromanoff[16], affording exclusively the *C*-α-D-glycosyl compound.



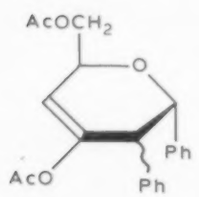
In several cases (Exps. 1, 2, 3, and 4), a small proportion of another product that had the same chromatographic behavior as **5** (already available in our laboratory[1]) was detected (g.l.c. and t.l.c.) in the reaction mixture. This compound was isolated by flash chromatography and was characterized by spectroscopy as **5** resulting from epimerization at C-4**. This epimerization was not mentionned by Goodwin *et al.*[10], but has been observed by Paulsen and Bünsch[14]. It is assumed that epimerization

*The nomenclature used to describe the configuration of *C*-glycosyl compounds is the same as that of glycosides.

**The carbohydrate numbering is used in this paper.

occurred at the enolate step resulting from a 1,4 addition, because the starting enone was recovered unchanged when not completely transformed (Exp. 1), and the degree of epimerization was not increased when the work-up was delayed. In the experiment with the higher-order, mixed cuprate ($Ph_2CuCNLi_2$), the degree of epimerization was significantly lower (3–5%) than in the experiment with the homocuprate (Ph_2CuLi) where the proportion of isomerization could reach 20% in some cases. In the presence of a strong field ligand (CN^-) it may be assumed that the intermediate enolate **7** is more ionic and, therefore, the rate of acylation is greater than that of proton transfer. The preservation of enolate regiospecificity resulted in a low percentage of C-4 epimerization (Exps. 2, 3, and 4). Finally, the epimerization was completely suppressed and the yield of overall isolated product was increased to 87% (Exp. 5) by introducing the trapping reagent together with the enone.

Although lithium salts were shown to influence the coupling of organocopper reagents with organic halides[17], no such effect was observed in our study (Exps. 2, 3, and 4). From enone **1** the best yield was obtained when the reaction was taken to completion at low temperature ($-50 \rightarrow -25°$; Exp. 5) in order to avoid any substitution at C-4 of the allylic acetate **4** by the organocopper reagent*. This reaction is well documented[19] and was applied to carbohydrate derivatives, but proceeds rather slower than 1,4-additions[12]. Indeed, in some cases in which the temperature was allowed to raise to 0°, a low-polar compound was isolated in small proportion ($\simeq$ 10%) and shown to be **8** by spectroscopy.



8

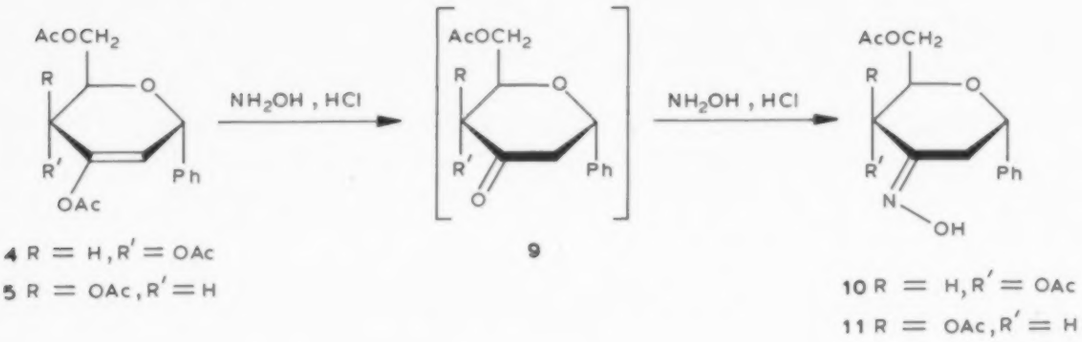
Concerning the organometallic reagent, the best results (yield and stereocontrol) were obtained with a higher-order, mixed organocuprate reagent prepared from commercially available solutions of phenyllithium and copper cyanide[20]. Although good results were obtained with a homocuprate (Ph_2CuLi), the reproducibility was low with this reagent and, sometimes, a low yield, or low stereoselectivity, or both were obtained without predictability.

4,6-Di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*threo*-hex-1-en-3-ulose (**2**) was next investigated. Under the best conditions the rate of phenylation was slightly lower but the yield of isolated *C*-α-D-glycosides **5** was about the same (Exp. 6). In this case, the epimerization at C-4 was not completely avoided, and **4** was isolated (yield 3%)

*Another advantage of a low temperature is that the possible reaction of the organocopper reagent with an enol ester[18] is slowed down, thus keeping the reaction simple and giving a high yield.

from the reaction mixture and characterized. This epimerization may be due to the quasi-axial position of $OCOCH_3$-4 in the intermediate.

The α-D configuration of the *C*-glycosylarenes was unambiguously proved by X-ray crystallography[2] for **5**, but, for the sirupy derivative **4**, additional proofs were needed, as examination of the coupling constants for vicinal sp^3–sp^2 carbon atoms may not be suficient[2]. Accordingly, **4** and **5** were transformed into the corresponding oximes **10** and **11** by action of an excess of hydroxylamine hydrochloride[21] *via* the nonisolated intermediate **9**. This high-yielding transformation being carried out under very mild conditions is a valuable tool for structure elucidation because the intermediate ketone is immediately quenched by an excess of reagent. The ^{1}H-n.m.r. data were easier to interpret as C-1 and C-2 are now sp^3, and spectral assignments were deduced from standard chemical-shifts and coupling-constant data and from extensive spin-decoupling experiments.



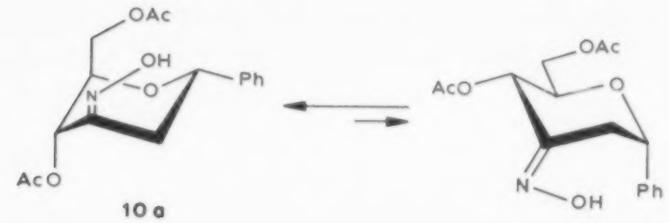
4 R = H, R′ = OAc
5 R = OAc, R′ = H

9

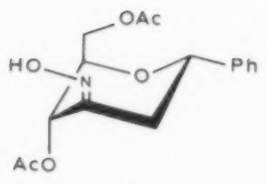
10 R = H, R′ = OAc
11 R = OAc, R′ = H

The crude oximes (**10** and **12**) prepared from **4** were shown to be a mixture of *Z,E* isomers (15 and 85%, respectively) by ^{1}H-n.m.r. [di($^2H_3$)methylsulfoxide]. According to previous work[22,23], the *E* configuration was attributed to the major isomer **10**, which was obtained in crystalline form. From **5**, a single *E* isomer **11** was obtained. In the ^{1}H-n.m.r. spectrum of oxime **11**, the H-1 signal is a doublet of doublet and the $J_{1,2}$ 3 and $J_{1,2}$ 6 Hz were too small for an axial–axial relationship between H-1 and H-2′, indicating that H-1 is not in an axial position. The value of 6 Hz, which may seem to be too large for an equatorial–axial coupling, has already been observed for other *C*-glycosyl compounds[24]. Therefore, only the $^4C_1$(D) conformation is in reasonable agreement with these data. Such conformation was confirmed by $J_{4,5}$ 2 Hz, which is in the range of expected value for the coupling between H-5*a* and H-4*e* of an hexopyranose derivative bearing an axial substituent at O-4 and a terminal CH_2OAc group[24]. Thus, the axial position of the phenyl group provided confirmation of the α-D configuration.

In the case of the oximes obtained from **4**, the H-1 signal of the major *E* isomer **10** was a doublet of doublet [($^2H_3$)Me_2SO] with $J_{1,2}$ 4.5 and $J_{1,2'}$ 8 Hz, suggesting an axial position for H-1 in a $^1C_4$(D) conformation (**10a**). The value $J_{4,5}$ 4.8 Hz was too small for an axial–axial relationship between these two protons, which is usually observed in the *gluco* series; this exclude the $^4C_1$(D) conformation.



10 a 10 b



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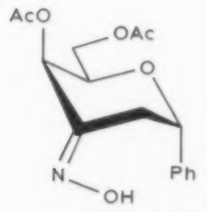

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It was also too large for a coupling constant between the equatorial protons in the $^1C_4$(D) conformation. These data favor a conformational equilibrium of compound **10** (**10a** and **10b**) in which the $^1C_4$(D) conformation preponderates. The occurrence of this unusual conformation is supported by the ^{1}H-n.m.r. data for the minor *Z* isomer **12** (examined in the presence of the *E* isomer **10**). In this case, the values $J_{1,2}$ 3.5, $J_{1,2'}$ 11, and $J_{4,5}$ 2 Hz were in agreement with a highly preponderating $^1C_4$(D) conformation having the phenyl group in equatorial position, thus confirming the α-D configuration at C-1. Since C-3 is sp^2, this conformation does not afford strong destabilizing 1,3-diaxial interactions. Similar stereochemical properties of *C*-glycosyl compounds were already observed for solutions in a polar solvent[24]. Furthermore, it can be noted that, in each conformation of **10** or **12**, one bulky group out of two (CH_2OAc or Ph) is in axial, whereas the other one is in equatorial position (Ph or CH_2OAc, respectively).

In compounds in which there is no anomeric effect to strongly influence the conformation, an important factor of stabilization may be the axial position of the acetoxy group in α-position to the sp^2 carbon atom of the oxime group. In this situation, a stabilizing overlap could occur between the σ* orbital of C-4–O and the π orbital of C=N, the axes of which are parallel. This effect resembles the anomeric effect in which the stabilizing effect occurs between the σ* orbital of C-1–O and a nonbinding doublet of the ring oxygen atom[25]. A similar effect was observed by Dupuis *et al.*[26] in the stabilization of radicals. This explanation would apply to α-substituted, sp^2 carbon atoms, such as α-halogenated ketone rather than the electrostatic repulsion of dipoles previously proposed[27].

The reaction of organocuprate with hex-1-enopyran-3-uloses in the presence of acetoxy groups provides an excellent method for the preparation of *C*-2-deoxy-α-D-glycosyl compounds, which are more difficult to prepare than β-D-glycosyl com-

pounds[5]. This reaction has several advantages, such as high yields, stereospecificity, and possibility of manipulations of the enol ester function present in the molecule.

EXPERIMENTAL

General methods. — Melting points were determined with a Thomas–Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer polarimeter. I.r. spectra (film or KBr disk) were recorded with a Unicam SP3-300 spectrophotometer, and ^{1}H-n.m.r. spectra with a Brucker WH-250 spectrometer (tetramethylsilane as internal standard). Gas chromatography (g.l.c.) was carried out with a Girdel 75 FD instrument fitted with a column (1 m) of 3% (w/w) *N*-phenyldiethanolamine succinate (PDEAS) on Chromosorb WAW DMCS. Analytical t.l.c. was performed on Merck aluminium precoated plates of Silica gel 60 F-245 with detection by u.v., and by spraying with 3M H_2SO_4 and heating. The following solvent systems were used; solvent *A* (2:1 diethyl ether–ligroin) and solvent *B* (1:1 diethyl ether–chloroform). Merck silica gel 60 (230–400 mesh) was used for flash chromatography. Oxolane was distilled from benzophenone–sodium immediately before use. Phenyllithium solutions were purchased from Aldrich and Fluka and standardized[28] before use. Copper(I) salts from Prolabo were used without purification. Elemental analyses were performed by the Service de Microanalyse of the Université P. et M. Curie.

Typical conjugate addition procedure exemplified by reaction of enone **1** *with higher-order cuprate. Preparation of (3,4,6-tri-*O*-acetyl-2-deoxy-*α*-*D*-*erythro*-hex-2-enopyranosyl)benzene* (**4**). — To a suspension of copper(I) cyanide (600 mg, 6.6 mmol), in anhydrous oxolane (6 mL) under Ar, was added a 2M solution of phenyllithium (6 mL, 12 mmol) at −50°. After 10 min of being stirred, the solution gave a negative Gilman test[29]. Under vigorous stirring, anhydrous oxolane solution (6 mL) containing enone **1** (684 mg, 3 mmol) and acetic anhydride (570 μL, 6 mmol) was added slowly *via* a syringe needle at such a rate that the temperature was maintained at −50°. Immediately, the dark-brown mixture became an orange homogenous solution. The temperature was allowed to rise up to (≃ 1 h), and maintained at −25°. After completion of the reaction was indicated by t.l.c. (solvent *A*), saturated NH_4Cl solution (2 mL) was added and the product extracted with diethyl ether (3 × 30 mL). The combined ether solutions were washed with saturated NH_4Cl solution (2 × 20 mL) and water (1 × 15 mL), dried ($MgSO_4$), and evaporated. The crude residue was analyzed by g.l.c. Flash chromatography of the residue with mixtures of diethyl ether–ligroin of increasing polarity afforded pure **4** (908 mg, 87%), colorless oil, $[\alpha]_D^{20}$ +69° (*c* 1.7, chloroform); lit.[1] $[\alpha]_D$ +69° (*c* 1.7, chloroform); R_F 0.50 (solvent *A*); r.t. 18.3 min at 140°; i.r. and ^{1}H-n.m.r. spectra were identical to those previously recorded[1].

Anal. Calc. for $C_{18}H_{20}O_7$ (348.34): C, 62.06; H, 5.79. Found: C, 61.82; H, 5.62.

*(3,4,6-Tri-*O*-acetyl-2-deoxy-*α*-*D*-threo-hex-2-enopyranosyl)benzene* (**5**). —

The same procedure used for the preparation of **4** was applied to enone **2** to afford **5** (865 mg, 83%), m.p. 126–126.5°, $[\alpha]_D^{20}$ −195° (*c* 1.63, chloroform); lit.[1] m.p. 126–126.5°, $[\alpha]_D^{20}$ −195° (*c* 1.63, chloroform); R_F 0.56 (solvent *A*); r.t. 16.2 min at 140°; i.r. and ^{1}H-n.m.r. spectra identical to those previously recorded[1].

Anal. Calc. for $C_{18}H_{20}O_7$ (348.34): C, 62.06; H, 5.79. Found: C, 62.08; H, 5.74.

Further elution gave 30 mg (3%) of **4**.

Typical procedure for the preparation of oximes. — The reaction was performed at room temperature. The *C*-glycosyl compound (1 mmol) and hydroxylamine hydrochloride (4 mmol) were dissolved in anhydrous pyridine (2.5 mL). After t.l.c. (solvent *B*) indicated completion of the reaction (≃ 15 h), water (5 mL) was added and the product extracted with chloroform (3 × 20 mL). The combined extracts were washed with M HCl (1 × 10 mL), 5% $NaHCO_3$ (1 × 10 mL), and water to neutral pH. After being dried ($MgSO_4$), the solution was evaporated under reduced pressure. The crude product was purified by crystallization or flash chromatography (1:1 diethyl ether–chloroform).

*(4,6-Di-*O*-acetyl-2-deoxy-*α*-*D*-*erythro*-hexopyranosyl-3-ulose oxime)benzene* (**10**). Yield 285 mg (89%), m.p. 89–90° (diethyl ether), $[\alpha]_D^{20}$ +112° (*c* 1.3, chloroform); R_F 0.51 (solvent *B*); ν_{max}^{KBr} 3380 (OH), 1740 (ester), and 1650 cm^{-1} (weak, C=N); ^{1}H-n.m.r. [($^2H_3$)Me_2SO]: δ 11.34 (s, 1 H, NOH), 7.24–7.46 (m, 5 H, arom.), 4.99 (dd, 1 H, $J_{1,2}$ 4.5, $J_{1,2'}$ 8 Hz, H-1), 3.0 (dd, 1 H, H-2*e*), 2.82 (dd, 1 H, $J_{2e,2a}$ 14 Hz, H-2*a*), 5.22 (d, 1 H, $J_{4,5}$ 4.8 Hz, H-4), 3.97–4.07 (m, 1 H, $J_{5,6a}$ 6.5 Hz, $J_{5,6b}$ 4 Hz, H-5), 4.35 (dd, 1 H, $J_{6a,6b}$ 12 Hz, H-6*a*), 4.12 (dd, 1 H, H-6*b*), and 2.02–2.06 (2 s, 2 $OCOCH_3$).

Anal. Calc. for $C_{16}H_{19}NO_6$ (321.33): C, 59.81; H, 5.96; N, 4.36. Found: C, 60.05; H, 6.13; N, 4.51.

*(4,6-Di-*O*-acetyl-2-deoxy-*α*-*D*-*threo*-hexopyranosyl-3-ulose oxime)benzene* (**11**). Yield 301 mg (94%), m.p. 112–112.5° (diethyl ether–hexane), $[\alpha]_D^{20}$ +175° (*c* 1.13, chloroform); R_F 0.51 (solvent *B*); ν_{max}^{KBr} 3350 (OH), 1750 (ester), and 1665 cm^{-1} (weak, C=N); ^{1}H-n.m.r. [($^2H_3$)Me_2SO]: δ 11.42 (s, 1 H, NOH), 7.29–7.41 (m, 5 H, arom.), 5.28 (dd, 1 H, $J_{1,2}$ 3 $J_{1,2'}$ 6 Hz, H-1), 3.44 (dd, 1 H, $J_{2e,2a}$ 15 Hz, H-2*e*), 2.7 (dd, 1 H, H-2*a*), 5.33 (d, 1 H, $J_{4,5}$ 2 Hz, H-4), 3.71–3.78 (m, 1 H, H-5), 4–4.15 (m, 2 H, H-6*a*,6*b*), and 1.99–2.10 (2 s, 2 $OCOCH_3$).

Anal. Calc. for $C_{16}H_{19}NO_6$ (321.33): C, 59.81; H, 5.96; N, 4.36. Found: C, 59.68; H, 5.98; N, 4.58.

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STEREOCONTROLLED PREPARATION OF C-2-DEOXY-α- AND -β-D-GLUCOPYRANOSYL COMPOUNDS FROM TRIBUTYL-(2-DEOXY-α- AND -β-D-GLUCOPYRANOSYL)STANNANES*

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ABSTRACT

Tributylstannyllithium treatment of 3,4,6-tri-*O*-benzyl-2-deoxy-α-D-*arabino*-hexopyranosyl chloride (**2**) provided selectively tributyl (3,4,6-tri-*O*-benzyl-2-deoxy-β-D-*arabino*-hexopyranosyl)stannane (**3**) in 85% yield. Isomeric tributyl (3,4,6-tri-*O*-benzyl-2-deoxy-α-D-*arabino*-hexopyranosyl)stannane (**6**) could be prepared in 70% yield by reductive lithiation of **2** and reaction with tributyltin chloride. Tin–lithium exchange reaction, performed on **3** and **6** with butyllithium in oxolane at −78°, generated the corresponding, configurationally stable 2-deoxy-β- and -α-D-hexopyranosyllithium compounds which reacted with electrophilic compounds with retention of configuration. Addition of these glycosyllithium reagents to prochiral carbonyl compounds gave variable degrees of facial selectivity. A significant diastereofacial discrimination (10:1) was observed by condensation of 3,4,6-tri-*O*-benzyl-2-deoxy-α-D-*arabino*-hexopyranosyllithium reagent with hexanal and isobutyraldehyde. The structure of all *C*-glycopyranosyl compounds obtained was established by ^{1}H-n.m.r. spectroscopy.

INTRODUCTION

Carbohydrate-based methods of synthesis have often proved to be very appropriate in the preparation of enantiomerically pure, natural and artificial compounds[2]. One particular area which has grown rapidly in the past few years is the synthesis of 2,6-dialkylated oxolane units (*C*-glycopyranosyl compounds). These structural systems are not only frequently found in a wide variety of natural products, but are also good starting points for other synthetic objectives in which stereocontrolled lengthening of a carbohydrate chain is needed. Reactions of carbon nucleophiles with the electrophilic anomeric center of carbohydrates are the most exploited routes to *C*-glycopyranosyl syntheses[3]. Less common

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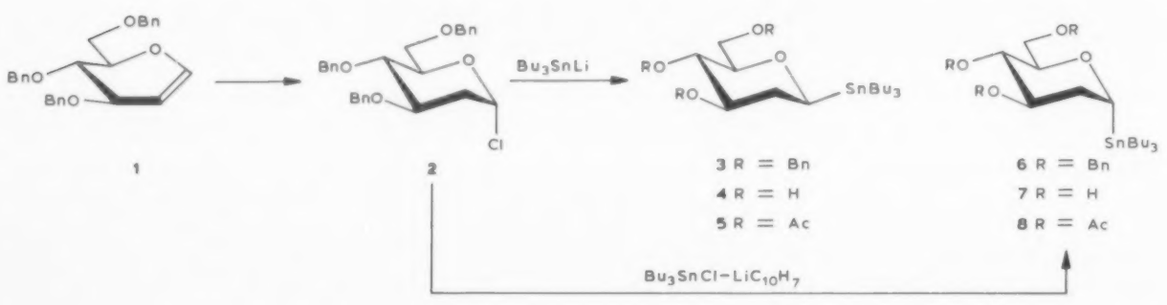
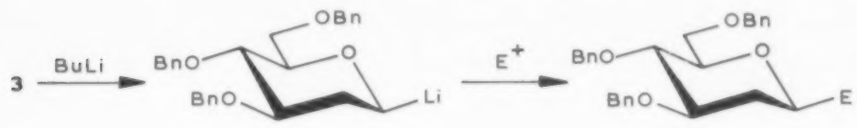
approaches may also be realized by use of a nucleophilic anomeric center. Thus, the efficient and stereocontrolled introduction of carbon side-chains has been described by use of either a stabilized nucleophilic intermediate derived from anomeric phosphonium salts[4], nitro[5] and phenylsulfonyl[6] sugar derivatives, and pentacarbonyl glycosylmanganese complexes[7], or 2-deoxy-D-glucopyranosyllithium reagents[8]. As part of an ongoing research program in this area, we report herein a stereocontrolled method for the preparation of *C*-glycopyranosyl compounds from tributyl (2-deoxy-D-glucopyranosyl)stannanes.

RESULTS AND DISCUSSION

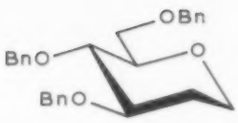
α-Alkoxy organostannanes, prepared by the addition of organotin nucleophiles to aldehydes or ketones[9], followed by immediate protection of the intermediate alcohol[10], have been shown to be useful precursors of α-alkoxy organolithium compounds through a fast, low-temperature, exchange reaction with alkyllithium reagents[10,11]. In addition, tin–lithium exchange on stereodefined α-alkoxy organostannanes occurs with retention of configuration and the tetrahydral lithiated compounds, thus formed, accept electrophiles with retention of configuration as well[12,13]. In view of these observations, a stereoselective anomeric trialkylstannylation of carbohydrates would provide, *via* the corresponding glycosyllithium reagents, a stereocontrolled route to *C*-glycopyranosyl compounds. Reaction of the tri-*O*-benzyl-D-glucal[14] **1** with hydrogen chloride in toluene[8,15] gave unstable 3,4,6-tri-*O*-benzyl-2-deoxy-α-D-*arabino*-hexopyranosyl chloride (**2**) which was treated immediately with tributylstannyllithium[10] in oxolane at 0°. The products formed were easily separated on a column of silica gel, providing the tributyl-β-D-glycosylstannane **3** as the major compound (85% from glucal **1**), along with a small proportion of its α-D anomer **6** (1.5% from **1**). The reaction of triorganotin–alkali reagents with organic halides is a well-known route for synthesis of tetraorganotin compounds[16]. That the substitution reaction on chloride **2** was indeed possible was strongly indicated by the preparation of 1-tributylstannyl-1-methoxyheptane from 1-chloro-1-methoxyheptane by Still[10]. The stereoselectivity observed (50~60:1) in favor of the β-D anomer **3** suggests a preponderant direct (SN2) displacement, although this statement must await further mechanistic investigation. The tributyl-α-D-glycosylstannane **6** was selectively obtained from chloride **2** by reductive lithia-





9

10 E = ^2H
11 E = CH(OH)Ph
12 E = $CH(OH)C_5H_{11}$
13 E = $CH(OH)CHMe_2$
14 E = COPh
15 E = COC_5H_{11}
16 E = $COCHMe_2$
17 E = $C(OH)Me_2$
18 E = 2-cyclohexen-1-ol-1-yl
19 E = C_4H_9



20

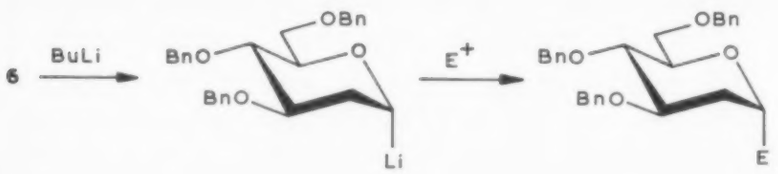
tion[8] with two equiv. of lithium naphthalenide in oxolane at −78°, followed by the addition of tributyltin chloride (70% from **1**). Hydrogenolytic removal of the benzyl groups of **3** and **6** gave triols **4** and **7**, converted into their triacetates **5** and **8**, respectively. The introduction, in equatorial position, of tin in compound **3** was readily indicated by the ^{1}H-n.m.r. data; the values of the vicinal coupling-constants of the ring protons (see Experimental section) suggested a $^4C_1$(D) chair conformation in which H-1 was axially oriented ($J_{1,2}$ 1.9 and 13.2 Hz). The stereochemical relation at C-1 in the α-D series could only be confirmed for **7** and **8**, where a $^4C_1$(D) chair-conformation was deduced from the ^{1}H-n.m.r. data with substantial differences in the $J_{1,2}$ values ($J_{1,2e}$ 1.2–4.2 Hz, and $J_{1,2a}$ 6.1–4.2 Hz). Satellites arising from coupling of H-1 with the ^{117}Sn and ^{119}Sn nuclei were only clearly resolved in the ^{1}H-n.m.r. spectra of triols **4** and **7**, and triacetates **5** and **8**. Great differences in the $J_{1,Sn}$ values, 16.3 and 16.2 Hz for **3** and **4** (β-D anomers), as compared to 27.2 and 26.9 Hz for **7** and **8** (α-D anomers), were observed.

Our attention was next turned to the use of glycosylstannanes **3** and **6** in *C*-glycosylation reactions. Treatment of the glycosylstannane **3** with butyllithium in oxolane at −78°, followed by addition of deuterium oxide, gave specifically the deuteriated derivative **10** in 74% yield. The introduction, in equatorial position, of a deuterium atom was confirmed by ^{1}H-n.m.r. spectroscopy showing the H-1 signal at δ 3.35 as a quartet ($J_{1,2e}$ 1.9 and $J_{1,2a}$ 12.4 Hz). Compound **10** most probably arose from the 2-deoxy-β-D-glucopyranosyllithium derivative **9**.

The specific formation of **10** showed that the stereochemical geometry was completely maintained throughout the sequence of reactions, both steps (tin–lithium exchange and electrophilic trapping) occurring with retention of configuration. The sequence of reactions performed with benzaldehyde, hexanal, and isobutyraldehyde afforded the expected diastereoisomeric products **11** (95%; isomeric ratio, 2:1), **12** (80%; isomeric ratio, 1:1), and **13** (80%; isomeric ratio, 3:1), respectively, in which the newly formed carbon–carbon bond was equatorial. These com-

pounds were accompanied by variable proportions of 1,5-anhydro-3,4,6-tri-*O*-benzyl-1,2-dideoxy-D-*arabino*-hexitol (**20**; 1–10%), probably resulting from the hydrolysis of the lithiated intermediate **9**. All diastereoisomeric mixtures formed were oxidized by pyridinium chlorochromate in dichloromethane[17] to give single ketones **14, 15**, and **16**. The configuration at the anomeric center of **14, 15**, and **16** was readily deduced from ^{1}H-n.m.r. spectra showing H-1 resonances at δ 4.32 (for **15**) to 5.19 (for **14**) as quartets with $J_{1,2}$ values 1.9–2.2 Hz ($J_{1,2e}$) and 12–12.2 Hz ($J_{1,2a}$) in a $^4C_1$(D) conformation. Glycosyllithium **9** also reacted with acetone to produce alcohol **17** and with 2-cyclohexenone in a 1,2-position to give allylic alcohol **18** as a 1:1 diastereoisomeric mixture. In the latter case, none of the corresponding 1,4-adduct could be detected. The reaction with butyl iodide gave, in low yield (39%), the *C*-butylglycoside **19**, as was the case with reactions using other alkyl iodides not described in this work. Large proportions of **20** (up to 52%) were formed, and it appears that the hydrogen transfer was preferred to alkylation, although the reason for this behavior has not yet been determined. In all reactions, exclusive formation of an equatorial carbon–carbon bond was observed, indicating the equatorial nature of the carbon–lithium bond of **9**. These results were not surprising in that strong stereoelectronic-stabilizing effects have already been demonstrated for similar stereochemical situations[18].

Similarly, treatment of tributyl-α-D-glycopyranosylstannane **6** with butyllithium in oxolane at −78°, and addition of deuterium oxide to the glycosyllithium derivative thus produced gave the deuteriated α-D anomer **22** which is identical to the product already described[8]. The actual conformation of the lithium reagent **21** is unknown, but it is possible that the lithium anomeric substituent, or the corresponding lone pair, prefers a (pseudo)equatorial orientation in order to avoid a destabilizing interaction with one of the nonbonding electron pairs of the ring oxygen atom[18] (reverse anomeric effect[19]). Coupling reactions using benzaldehyde, hexanal, and isobutyraldehyde afforded the diastereoisomeric alcohols **23** (65%; ratio 3:1), **24** (74%; ratio, 10:1), and **25** (85%; ratio 10:1), respectively, together with **20**. Pyridinium chlorochromate oxidation of **23, 24**, and **25** occurred without isomerization to give the single ketones **26** (69%), **27** (73%), and **28** (89%),



21

22 E = D
23 E = CH(OH)Ph
24 E = $CH(OH)C_5H_{11}$
25 E = $CH(OH)CHMe_2$
26 E = COPh
27 E = COC_5H_{11}
28 E = $COCHMe_2$

respectively. Examination of the ^{1}H-n.m.r. parameters of **23, 24**, and **25** indicated a substantial conformational deviation from the usual $^4C_1$(D) conformation (see Experimental section), which was especially noticeable for the minor isomers, as for instance for **23** where vicinal-coupling constant values of 4.6 Hz for $J_{3,4}$ and $J_{4,5}$, and 3.9 and 9.0 Hz for $J_{1,2}$ were found. This conformational distortion, probably due to steric interaction between the sugar ring and the α-hydroxy-alkyl or -aryl side-chain was no longer perceptible in the ^{1}H-n.m.r. spectra of ketones **26, 27**, and **28**, where coupling constant values of 8.3–8.9 Hz ($J_{3,4}$ and $J_{4,5}$), 10.3–10.8 Hz ($J_{2a,3}$), 2.1–3.0 Hz ($J_{1,2e}$), and 5.8 Hz ($J_{1,2a}$) were observed, values consistent with a $^4C_1$(D) conformation.

As already established[6,8,20], such kinetically-generated lithiated compounds as **21** are configurationally stable under the conditions used (oxolane, −78°). The selectivity of the attack at the carbonyl group by the glycosyllithium reagent **9** was low (ratio 1:1–3:1), but became significant in the condensation of glycosyllithium **21** with hexanal and isobutyraldehyde (ratio 10:1*), although the like or unlike[21] nature of the stereochemical outcome is presently unknown. More examples are needed to delineate the synthetic usefulness of the facial discrimination of these asymmetric carbanions in their addition reactions to prochiral or chiral carbonyl compounds. High levels of diastereofacial selectivity would, therefore, allow the stereoselective construction of two chiral centers in a single synthetic operation.

EXPERIMENTAL

General methods. — Melting points were determined for capillary tubes with a Büchi apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer Model 141 polarimeter at the sodium D-line at 22±2°. ^{1}H-N.m.r. spectra were recorded with a Perkin–Elmer R-32 (90 MHz) or Bruker AM-300 (300 MHz) spectrometer for solutions in $CDCl_3$ (internal Me_4Si) unless otherwise stated. Mass spectra were recorded with a Ribermag R-10-10 instrument in the desorption chemical-ionization (d.c.i.) mode using ammonia as the reagent gas. All solvents and reagents were purified and dried according to standard procedures[22]. Tributylstannyllithium was prepared by the addition of butyllithium to commercial hexabutylditin in oxolane (0°, 15 min), according to Still[10]. Solution transfers were conducted under dry Ar by standard syringe techniques. T.l.c. was performed on Silica gel 60-F_{254} (Merck) with detection by quenching of fluorescence and by charring with H_2SO_4. For column chromatography, the loading was in the range 1:20–1:50 on Silica gel 60 (Merck, 63–200 μm) which was used without pre-treatment. Elemental analyses were performed by the Service Central de Micro-Analyse du Centre National de la Recherche Scientifique.

*Erroneously reported as 3:1 for hexanal[1].

*Tributyl-(3,4,6-tri-*O*-benzyl-2-deoxy-β-*D*-arabino-hexopyranosyl)stannane* (**3**). — 1,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enitol (**1**) was prepared essentially as described by Blackburne *et al.*[14], by benzylation (NaH, benzyl bromide) in anhydrous *N,N*-dimethylformamide, m.p. 57°, $[\alpha]_D^{22}$ −2.7° (*c* 1.89, chloroform); lit.[14] m.p. 57–57.5°, $[\alpha]_D$ −2.9° (chloroform); lit.[23] m.p. 55°, $[\alpha]_D$ −2.7° (chloroform). Dry HCl was bubbled through a stirred solution of **1** (2.39 g, 5.74 mmol) in anhydrous toluene (10 mL) at 0° for 15 min. Excess HCl was eliminated by Ar bubbling and the solution was concentrated under reduced pressure. After several co-evaporations with toluene, the colorless syrup of 3,4,6-tri-*O*-benzyl-2-deoxy-α-D-*arabino*-hexopyranosyl chloride (**2**) was dried under high-vacuum (1 h), and used immediately in the next step.

To a stirred solution of **2** in anhydrous oxolane (6 mL) under Ar at 0° was added, in the course of 20 min, a 0.5M solution of freshly prepared tributylstannyllithium in oxolane (17.2 mL, 8.6 mmol, 1.5 equiv.). After 1.5 h at 0°, NH_4Cl was added and the mixture was diluted with ethyl ether (100 mL) and water (30 mL). The organic phase was washed twice with sat. aqueous NH_4Cl solution, dried ($MgSO_4$), and evaporated. Column chromatography (hexane, then hexane–ethyl acetate, 6:1) of the residue provided **3** (3.46 g, 85%), colorless syrup, $[\alpha]_D^{22}$ −9.3° (*c* 1.76, chloroform); ^{1}H-n.m.r.: δ 1.84 (ddd, 1 H, $J_{2a,3}$ 10.2, $J_{2a,2e}$ 13.0, $J_{1,2a}$ 13.2 Hz, H-2*a*), 2.13 (ddd, 1 H, $J_{1,2e}$ 1.9, $J_{2e,3}$ 4.9, $J_{2a,2e}$ 13.0 Hz, H-2*e*), 3.24 (dt, 1 H, $J_{5,6a} = J_{5,6b}$ 3.0, $J_{4,5}$ 8.9 Hz, H-5), 3.49 (t, 1 H, $J_{3,4} = J_{4,5}$ 8.9 Hz, H-4), 3.57 (ddd, 1 H, $J_{2e,3}$ 4.9, $J_{3,4}$ 8.9, $J_{2a,3}$ 10.2 Hz, H-3), 3.63 (dd, 1 H, $J_{1,2e}$ 1.9, $J_{1,2a}$ 13.2 Hz, H-1), and 3.71 (m, 2 H, H-6a,6b); m.s.: *m/z* 597 (17), 599 (28), 601 (37), (M^+ −OBn), 647 (39), 649 (77), and 651 (100) (M^+ −Bu).

Anal. Calc. for $C_{39}H_{56}O_4Sn$: C, 66.20; H, 7.98. Found: C, 66.48; H, 8.15.

Further elution of the column yielded the anomer **6** (60 mg, 1.5%), identical to the compound described later.

*Tributyl-(2-deoxy-β-*D*-arabino-hexopyranosyl)stannane* (**4**). — A solution of stannane **3** (143 mg, 0.20 mmol) in methanol (2 mL) containing 10% Pd–C (~10 mg) under H_2 was stirred for 1 h at room temperature. The mixture was filtered through Celite, and the insoluble material washed with several portions of methanol. Evaporation to dryness of the combined filtrate and washings gave a residue which was purified by column chromatography (2:3 dichloromethane–ethyl acetate) to yield **4** (77 mg, 87%), colorless syrup, $[\alpha]_D^{22}$ −8.5° (*c* 1.32, chloroform); ^{1}H-n.m.r.: δ 1.83 (dt, 1 H, $J_{2a,3}$ 10.8, $J_{1,2a} = J_{2a,2e}$ 13.2 Hz, H-2*a*), 2.03 (ddd, 1 H, $J_{1,2e}$ 2.2, $J_{2e,3}$ 5.0, $J_{2e,2a}$ 13.2 Hz, H-2*e*), 3.11 (ddd, 1 H, $J_{5,6b}$ 3.7, $J_{5,6a}$ 4.6, $J_{4,5}$ 8.9 Hz, H-5), 3.39 (t, 1 H, $J_{3,4} = J_{4,5}$ 8.9 Hz, H-4), 3.585 (ddd, 1 H, $J_{2e,3}$ 5.0, $J_{3,4}$ 8.9, $J_{2a,3}$ 10.8 Hz, H-3), 3.73 (dd, 1 H, $J_{5,6a}$ 4.6, $J_{6a,6b}$ 11.8 Hz, H-6a), 3.78 (dd, 1 H, $J_{1,2e}$ 2.2, $J_{1,2a}$ 13.2 Hz, H-1), and 3.815 (dd, 1 H, $J_{5,6b}$ 3.7, $J_{6a,6b}$ 11.8 Hz, H-6b); ^{117,119}Sn satellites for H-1: $J_{Sn,1}$ 16.3 Hz.

Anal. Calc. for $C_{18}H_{38}O_4Sn$: C, 49.45; H, 8.76. Found: C, 49.65; H, 8.92.

*Tributyl-(3,4,6-tri-*O*-acetyl-2-deoxy-β-*D*-arabino-hexopyranosyl)stannane* (**5**). — Acetylation of **4** (61 mg, 0.14 mmol) under standard conditions (acetic

anhydride, pyridine) afforded, after column chromatography (5:1 hexane–ethyl acetate), **5** (74 mg, 93%), syrup, $[\alpha]_D^{22}$ −25° (*c* 2.9, chloroform); ^{1}H-n.m.r.: δ 1.93 (dt, 1 H, $J_{2a,3}$ 10.6, $J_{1,2a} = J_{2a,2e}$ 13.2 Hz, H-2*a*), 2.03–2.04 (3 s, 9 H, 3 $COCH_3$), 2.14 (ddd, 1 H, $J_{1,2e}$ 2.1, $J_{2e,3}$ 5.0, $J_{2a,2e}$ 13.2 Hz, H-2*e*), 3.40 (ddd, 1 H, $J_{5,6a}$ 2.6, $J_{5,6b}$ 5.2, $J_{4,5}$ 9.3 Hz, H-5), 3.725 (dd, 1 H, $J_{1,2e}$ 2.1, $J_{1,2a}$ 13.2 Hz, H-1), 4.04 (dd, 1 H, $J_{5,6a}$ 2.6, $J_{6a,6b}$ 12.1 Hz, H-6a), 4.14 (dd, 1 H, $J_{5,6b}$ 5.2, $J_{6a,6b}$ 12.1 Hz, H-6b), and 4.89 (ddd, 1 H, $J_{2e,3}$ 5.0, $J_{3,4} = J_{4,5}$ 9.3 Hz, H-4); ^{117,119}Sn satellites for H-1: $J_{Sn,1}$ 16.2 Hz.

Anal. Calc. for $C_{24}H_{44}O_7Sn$: C, 51.17; H, 7.87. Found: C, 51.11; H, 8.16.

*Tributyl-(3,4,6-tri-*O*-benzyl-2-deoxy-α-*D*-arabino-hexopyranosyl)stannane* (**6**). — Chloride **2**, prepared from **1** (532 mg, 1.28 mmol) as described above, was dissolved in anhydrous oxolane (10 mL) and the solution chilled to −78° under Ar. Lithium naphthalenide (2.7 mL of a M oxolane solution[24]; 2.7 mmol, 2.1 equiv.) was added in the course of 5 min. To the dark-red solution was immediately added tributyltin chloride (0.7 mL, 2.56 mmol, 2 equiv.), and the mixture was stirred for 15 min at −78°. After addition of NH_4Cl, the mixture was diluted with ethyl ether (50 mL), and water (20 mL). The organic phase was washed with sat. aqueous NH_4Cl, dried ($MgSO_4$), and evaporated. Column chromatography (9:1 hexane–ethyl acetate) of the residue gave **6** (631 mg, 70%), colorless oil, $[\alpha]_D^{22}$ +26° (*c* 5.53, chloroform); ^{1}H-n.m.r.: δ 2.17 (m, 2 H, H-2a,2b), 3.16 (ddd, 1 H, $J_{5,6a}$ 2.1, $J_{5,6b}$ 4.1, $J_{4,5}$ 8.5 Hz, H-5), 3.50 (t, 1 H, $J_{3,4} = J_{4,5}$ 8.5 Hz, H-4), 3.55 (m, 1 H, H-3), 3.64 (dd, 1 H, $J_{5,6a}$ 2.1, $J_{6a,6b}$ 10.2 Hz, H-6a), 3.72 (dd, 1 H, $J_{5,6b}$ 4.1, $J_{6a,6b}$ 10.2 Hz, H-6b), and 4.56 (m, 1 H, H-1); m.s.: *m/z* 647 (38), 649 (77), 651 (100), (M^+ −Bu), 722 (12), 724 (22), and 726 (30) (M^+ +18).

Anal. Calc. for $C_{39}H_{56}O_4Sn$: C, 66.20; H, 7.98. Found: C, 66.16; H, 7.99.

*Tributyl-(2-deoxy-α-*D*-arabino-hexopyranosyl)stannane* (**7**) *and tributyl-(3,4,6-tri-*O*-acetyl-2-deoxy-α-*D*-arabino-hexopyranosyl)stannane* (**8**). — Hydrogenolysis of **6** (50 mg, 0.07 mmol) in ethyl acetate (2 mL) under the conditions described for the preparation of **4** gave, after purification by column chromatography (20:1 dichloromethane–methanol), **7** (22 mg, 71%), colorless syrup, $[\alpha]_D^{22}$ +33° (*c* 0.36, chloroform); ^{1}H-n.m.r.: δ 2.08 (ddd, 1 H, $J_{1,2e}$ 1.2, $J_{2e,3}$ 5.4, $J_{2a,2e}$ 13.1 Hz, H-2*e*), 2.17 (ddd, 1 H, $J_{1,2a}$ 6.1, $J_{2a,3}$ 10.8, $J_{2a,2e}$ 13.1 Hz, H-2*a*), 3.03 (dt, 1 H, $J_{5,6a} = J_{5,6b}$ 4.0, $J_{4,5}$ 9.0 Hz, H-5), 3.41 (t, 1 H, $J_{3,4} = J_{4,5}$ 9.0 Hz, H-4), 3.59 (ddd, 1 H, $J_{2e,3}$ 5.4, $J_{3,4}$ 9.0, $J_{2a,3}$ 10.8 Hz, H-3), 3.81 (m, 2 H, H-6a,6b), and 4.52 (dd, 1 H, $J_{1,2e}$ 1.2, $J_{1,2a}$ 6.1 Hz, H-1); ^{117,119}Sn satellites for H-1: $J_{Sn,1}$ 27.2 Hz.

Acetylation by standard conditions of **7** (104 mg, 0.24 mmol) afforded **8** (119 mg, 89%), colorless syrup, $[\alpha]_D^{22}$ +43° (*c* 2.69, chloroform); ^{1}H-n.m.r.: δ 2.03, 2.055, and 2.08 (3 s, 9 H, 3 CH_3CO), 2.21 (m, 2 H, H-2a,2b), 2.85 (ddd, 1 H, $J_{5,6a}$ 2.4, $J_{5,6b}$ 5.8, $J_{4,5}$ 8.9 Hz, H-5), 4.45 (dd, 1 H, $J_{5,6a}$ 2.4, $J_{6a,6b}$ 12.1 Hz, H-6a), 4.29 (dd, 1 H, $J_{5,6b}$ 5.8, $J_{6a,6b}$ 12.1 Hz, H-6b), 4.53 (t, 1 H, $J_{1,2} = J_{1,2'}$, 4.2 Hz, H-1), and 4.91 (m, 2 H, H-3,4); ^{117,119}Sn satellites for H-1: $J_{Sn,1}$ 26.9 Hz.

Anal. Calc. for $C_{24}H_{44}O_7Sn$: C, 51.17; H, 7.87. Found: C, 51.55; H, 7.94.

General procedure for the C–C bond formation from stannanes **3** *and* **6**. — To a stirred solution of stannane **3** or **6** in anhydrous oxolane (1.5 mL/mmol) at −78°

under Ar was added butyllithium (1.6M in hexane, 1.2 equiv.). After stirring for 2 min at −78°, the electrophile (1.2 equiv.) was added neat or in oxolane solution (1 mL/mmol). The solution was then treated with NH_4Cl after being stirred for an appropriate period of time at −78° under Ar (usually 0.5 h). The mixture was diluted with ethyl ether and water, and the organic phase extracted twice with sat. aqueous NH_4Cl, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by chromatography.

*(1S)-1,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-*D*-(1-^{2}H)*arabino-*hexitol* (**10**). — Reaction of **3** (56.5 mg, 0.08 mmol) and D_2O (5 μL) under the conditions described above gave, after column chromatography (6:1 hexane–ethyl acetate), **10** (24.5 mg, 74%), colorless syrup, $[\alpha]_D^{22}$ +21° (*c* 2.07, chloroform); ^{1}H-n.m.r.: δ 1.70 (dt, 1 H, $J_{1,2a}$ 12.4, $J_{2a,2e} \simeq J_{2a,3} \simeq$ 13.0 Hz, H-2*a*), 2.07 (ddd, 1 H, $J_{1,2e}$ 1.9, $J_{2e,3}$ 5.0, $J_{2a,2e}$ 13.0 Hz, H-2*e*), 3.34 (m, 1 H, H-5), 3.35 (dd, 1 H, $J_{1,2e}$ 1.9, $J_{1,2a}$ 12.4 Hz, H-2*a*), 3.49 (t, 1 H, $J_{3,4} = J_{4,5}$ 9.0 Hz, H-4), 3.62 (ddd, $J_{2e,3}$ 5.0, $J_{3,4}$ 9.0, $J_{2a,3}$ 13.2 Hz, H-3), and 3.68 (m, 2 H, H-6a,6b).

Anal. Calc. for $C_{27}H_{29}DO_4$: C, 77.30; H, 7.45. Found: C, 77.31; H, 7.56.

*Phenyl (3,4,6-tri-*O*-benzyl-2-deoxy-β-*D*-arabino-hexopyranosyl) ketone* (**14**). — The general procedure with **3** (58 mg, 0.08 mmol) and benzaldehyde (9 μL, 0.10 mmol, 1.2 equiv.) afforded, after column chromatography (4:1 toluene–ethyl acetate), phenyl-(3,4,6-tri-*O*-benzyl-2-deoxy-β-D-*arabino*-hexopyranosyl)methanol (**11**; 41 mg, 95%), mixture of isomers, colorless syrup; ^{1}H-n.m.r. (selected data): (major isomer) δ 1.61 (dt, 1 H, $J_{1,2a} = J_{2a,3}$ 11.5, $J_{2a,2e}$ 12.9 Hz, H-2*a*) and 1.88 (ddd, 1 H, $J_{1,2e}$ 2.1, $J_{2e,3}$ 5.1, $J_{2a,2e}$ 12.9 Hz, H-2*e*); (minor isomer) δ 1.40 (dt, 1 H, $J_{1,2a} = J_{2a,3}$ 11.5, $J_{2a,2e}$ 12.9 Hz, H-2*a*) and 1.77 (ddd, 1 H, $J_{1,2e}$ 1.9, $J_{2e,3}$ 4.3, $J_{2a,2e}$ 12.9 Hz, H-2*e*); isomeric ratio, 2:1.

A solution of **11** (35 mg, 67 μmol) in dichloromethane (1 mL) was added to a stirred solution of pyridinium chlorochromate (43 mg, 0.20 mmol, 3 equiv.) in dichloromethane (1 mL) containing molecular sieves (4A) and sodium acetate (28 mg). Stirring was continued until the oxidation was complete (t.l.c.). Ethyl ether (2 mL) was added, the suspension was then stirred for an additional 15 min and filtered through a bed of silica gel, and the insoluble material was washed several times with ethyl ether. Evaporation of the combined filtrate and washings left a residue which was purified by column chromatography (3:1 hexane–ethyl acetate) to afford **14** (25 mg, 72%), colorless syrup, $[\alpha]_D^{22}$ +7° (*c* 0.91, chloroform); ^{1}H-n.m.r.: δ 1.85 (dt, 1 H, $J_{1,2a} \simeq J_{2a,3} \simeq$ 12, $J_{2a,2e}$ 13.0 Hz, H-2*a*), 2.49 (ddd, 1 H, $J_{1,2e}$ 1.9, $J_{2e,3}$ 5.0, $J_{2a,2e}$ 13.0 Hz, H-2*e*), 3.57 (t, 1 H, $J_{3,4} = J_{4,5}$ 8.9 Hz, H-4), 3.64 (ddd, 1 H, $J_{5,6a}$ 1.6, $J_{5,6b}$ 4.9, $J_{4,5}$ 8.9 Hz, H-5), 3.71 (dd, 1 H, $J_{5,6a}$ 4.9, $J_{6a,6b}$ 11.0 Hz, H-6a), 3.80 (dd, 1 H, $J_{5,6b}$ 1.6, $J_{6a,6b}$ 11.0 Hz, H-6b), 3.82 (m, 1 H, H-3), and 4.58 (dd, 1 H, $J_{1,2e}$ 1.9, $J_{1,2a}$ 12.4 Hz, H-1).

Anal. Calc. for $C_{34}H_{34}O_5$: C, 78.14; H, 6.56. Found: C, 78.18; H, 6.76.

*1-(3,4,6-Tri-*O*-benzyl-2-deoxy-β-*D*-arabino-hexopyranosyl)-1-hexanone* (**15**). — The general procedure with **3** (78 mg, 0.11 mmol) and hexanal (16 μL, 0.13 mmol, 1.2 equiv.) gave, after column chromatography (9:1 toluene–ethyl acetate),

1-(3,4,6-tri-*O*-benzyl-2-deoxy-β-D-*arabino*-hexopyranosyl)-1-hexanol as a mixture of isomers (**12**; 46 mg, 80%), colorless syrup; ^{1}H-n.m.r. (selected data): δ 1.59 (~q, *J* ~12 Hz, H-2*a* one isomer), 2.10 (m, 1 H, H-2*e* both isomers), 2.17 (bs, OH), 2.58 (bs, OH), 3.20 (ddd, $J_{1,2e}$ 1.7, $J_{1,CH(OH)}$ 6.6, $J_{1,2a}$ 11.0 Hz, H-1 one isomer), 3.31 (ddd, $J_{1,2e}$ 1.7, $J_{1,CH(OH)}$ 3.6, $J_{1,2a}$ 11.0 Hz, H-1 other isomer), 3.40 (m, 1 H, H-5), 3.67 (m, 1 H, H-3), and 3.72 (m, 2 H, H-6a,6b); isomeric ratio, 1:1.

Oxidation of **12** (62 mg, 0.12 mmol) by the procedure used for **11** gave, after column chromatography (9:1 toluene–ethyl acetate), **15** (59 mg, 94%), colorless syrup, $[\alpha]_D^{22}$ +31° (*c* 1.53, chloroform); ^{1}H-n.m.r.: δ 0.89 (t, 3 H, *J* 6.9 Hz, CH_3), 1.30 (m, 4 H, 2 CH_2), 1.48 (dt, 1 H, $J_{1,2a} = J_{2a,3}$ 12.1, $J_{2e,2a}$ 13.0 Hz, H-2*a*), 1.57 (m, 2 H, CH_2), 2.45 (ddd, 1 H, $J_{1,2e}$ 2.3, $J_{2e,3}$ 4.9, $J_{2e,2a}$ 13.0 Hz, H-2*e*), 2.65 (t, 2 H, *J* 7.2 Hz, CH_2CO), 3.44 (ddd, 1 H, $J_{5,6a}$ 2.2, $J_{5,6b}$ 4.0, $J_{4,5}$ 9.6 Hz, H-5), 3.50 (dd, 1 H, $J_{3,4}$ 7.9, $J_{4,5}$ 9.6 Hz, H-4), 3.69 (ddd, 1 H, $J_{2e,3}$ 4.9, $J_{3,4}$ 7.9, $J_{2a,3}$ 12.1 Hz, H-3), 3.75 (m, 2 H, H-6a,6b), and 3.79 (dd, 1 H, $J_{1,2e}$ 2.3, $J_{1,2a}$ 12.1 Hz, H-1).

Anal. Calc. for $C_{33}H_{42}O_5$: C, 76.72; H, 7.80. Found: C, 76.77; H, 7.83.

*2-Methyl-1-(3,4,6-tri-*O*-benzyl-2-deoxy-β-*D*-arabino-hexopyranosyl)-1-propanone* (**16**). — The general procedure with **3** (205 mg, 0.29 mmol) and isobutyraldehyde (32 μL, 0.35 mmol, 1.2 equiv.) gave, after column chromatography (4:1 dichloromethane–ethyl acetate), 2-methyl-1-(3,4,6-tri-*O*-benzyl-2-deoxy-β-D-*arabino*-hexopyranosyl)-1-propanol as a mixture of isomers (**13**; 113 mg, 80%), colorless syrup; ^{1}H-n.m.r. (selected data): (major isomer) δ 2.05 (ddd, $J_{1,2e}$ 2.1, $J_{2e,3}$ ~5, $J_{2a,2e}$ ~13 Hz, H-2*e*); (minor isomer) δ 2.16 (ddd, $J_{1,2e}$ ~2, $J_{2e,3}$ ~4, $J_{2a,2e}$ 12.8 Hz, H-2*e*); isomeric ratio, 3:1.

Oxidation of **13** (89 mg, 0.18 mmol) according to the procedure used for **11** gave, after column chromatography (50:1 dichloromethane–ethyl acetate), **16** (71 mg, 80%), colorless syrup, $[\alpha]_D^{22}$ +24.5° (*c* 2.53, dichloromethane); ^{1}H-n.m.r.: δ 1.10 and 1.11 (2 d, 6 H, *J* 7.0 Hz, 2 CH_3), 1.51 (~q, 1 H, $J_{2a,3}$ 11.2, $J_{1,2a}$ 12.2, $J_{2a,2e}$ 13.1 Hz, H-2*a*), 2.50 (ddd, 1 H, $J_{1,2e}$ 2.2, $J_{2e,3}$ 4.9, $J_{2a,2e}$ 13.1 Hz, H-2*e*), 3.21 (h, 1 H, *J* 7.0 Hz, $CHMe_2$), 3.45 (ddd, 1 H, $J_{5,6a}$ 2.2, $J_{5,6b}$ 3.9, $J_{4,5}$ 9.6 Hz, H-5), 3.515 (dd, 1 H, $J_{3,4}$ 8.0, $J_{4,5}$ 9.6 Hz, H-4), 3.70 (ddd, 1 H, $J_{2e,3}$ 4.9, $J_{3,4}$ 8.0, $J_{2a,3}$ 11.2 Hz, H-3), 3.76 (m, 2 H, H-6a,6b), and 3.89 (dd, 1 H, $J_{1,2e}$ 2.2, $J_{1,2a}$ 12.2 Hz, H-1).

Anal. Calc. for $C_{31}H_{36}O_5$: C, 76.20; H, 7.43. Found: C, 76.35; H, 7.44.

*1-Methyl-1-(3,4,6-tri-*O*-benzyl-2-deoxy-β-*D*-arabino-hexopyranosyl)-1-ethanol* (**17**). — The general procedure with **3** (300 mg, 0.42 mmol) and acetone (48 μL, 0.63 mmol, 1.5 equiv.) gave, after column chromatography (5:1 dichloromethane–ethyl acetate), **17** (122 mg, 60%), m.p. 58–60° (pentane–chloroform), $[\alpha]_D^{22}$ +14° (*c* 1.9, chloroform); ^{1}H-n.m.r.: δ 1.21 and 1.24 (2 s, 6 H, 2 CH_3), 1.51 (~q, 1 H, $J_{2a,3}$ 11.3, $J_{1,2a}$ 11.9, $J_{2a,2e}$ 12.7 Hz, H-2*a*), 2.16 (ddd, 1 H, $J_{1,2e}$ 1.9, $J_{2e,3}$ 5.0, $J_{2a,2e}$ 12.7 Hz, H-2*e*), 3.20 (dd, 1 H, $J_{1,2e}$ 1.9, $J_{1,2a}$ 11.9 Hz, H-1), 3.45 (dt, 1 H, $J_{5,6a} = J_{5,6b}$ 3.0, $J_{4,5}$ 9.5 Hz, H-5), 3.52 (dd, 1 H, $J_{3,4}$ 8.1, $J_{4,5}$ 9.5 Hz, H-4), 3.70 (ddd, 1 H, $J_{2e,3}$ 5.0, $J_{3,4}$ 8.1, $J_{2a,3}$ 11.3 Hz, H-3), and 3.76 (m, 2 H, H-6a,6b).

Anal. Calc. for $C_{30}H_{36}O_5$: C, 75.60; H, 7.61. Found: C, 75.68; H, 7.70.

*(1RS)-(1-3,4,6-Tri-*O*-benzyl-2-deoxy-β-*D*-arabino-hexopyranosyl)-2-cyclo-*

hexen-1-ol (**18**). — The general procedure with **3** (405 mg, 0.57 mmol) and 2-cyclohexen-1-one (83 μL, 0.85 mmol, 1.5 equiv.) gave, after column chromatography (2:1 hexane–ethyl acetate), **18** (192 mg, 65%) as a mixture of isomers, colorless syrup; ^{1}H-n.m.r.: δ 1.55 and 1.56 (2 q, 1 H, J ~12 Hz, H-2*a*), 1.61–2.07 (m, 6 H, 3 CH_2 cyclohexenyl), 2.12 and 2.17 (2 ddd, 1 H, $J_{1,2e}$ 2.1, $J_{2e,3}$ 5.1, $J_{2a,2e}$ 13.0 Hz, H-2*e*), 2.48 and 2.65 (2 bs, 1 H, OH), 3.26 and 3.30 (2 dd, 1 H, $J_{1,2e}$ 2.1, $J_{1,2a}$ 10.5 Hz, H-1), 3.42 (m, 1 H, H-5), 3.49 and 3.50 (2 dd, 1 H, $J_{3,4}$ 8.3, $J_{4,5}$ 9.7 Hz, H-4), 3.67 (m, 1 H, H-3), 3.73 (m, 2 H, H-6a,6b), 5.67, and 5.71 (m, 1 H, $J_{CH=CH}$ 10.2 Hz, H vinylic), and 5.92 (m, 1 H, H vinylic); isomeric ratio, 1:1.

Anal. Calc. for $C_{33}H_{38}O_5$: C, 77.01; H, 7.44. Found: C, 77.27; H, 7.74.

1-(3,4,6-Tri-O-benzyl-2-deoxy-β-D-arabino-hexopyranosyl)butane (**19**). — The general procedure with **3** (331 mg, 0.47 mmol) and butyl iodide (80 μL, 0.70 mmol, 1.5 equiv.) gave, after column chromatography (15:1 hexane–ethyl acetate), **19** (86 mg, 39%) as a colorless syrup, $[\alpha]_D^{22}$ +6.7° (*c* 3.55, chloroform); ^{1}H-n.m.r.: δ 0.90 (t, 3 H, J 7.0 Hz, CH_3), 1.25–1.51, 1.62 (m, 6 H, 3 CH_2 butyl), 1.38 (dt, 1 H, $J_{1,2a} = J_{2a,3}$ 11.3, $J_{2a,2e}$ 12.9 Hz, H-2*a*), 2.14 (ddd, 1 H, $J_{1,2e}$ 1.9, $J_{2e,3}$ 5.0, $J_{2a,2e}$ 12.9 Hz, H-2*e*), 3.31 (m, 1 H, $J_{1,2e}$ 1.9, J_{1,CH_2} 5.2, 7.1, $J_{1,2a}$ 11.3 Hz, H-1), 3.37 (ddd, 1 H, $J_{5,6b}$ 2.1, $J_{5,6a}$ 4.4, $J_{4,5}$ 9.6 Hz, H-5), 3.47 (dd, 1 H, $J_{3,4}$ 8.6, $J_{4,5}$ 9.6 Hz, H-4), 3.64 (ddd, 1 H, $J_{2e,3}$ 5.0, $J_{3,4}$ 8.6, $J_{2a,3}$ 11.4 Hz, H-3), 3.68 (dd, 1 H, $J_{5,6a}$ 4.4, $J_{6a,6b}$ 10.7 Hz, H-6a), and 3.74 (dd, 1 H, $J_{5,6b}$ 2.1, $J_{6a,6b}$ 10.7 Hz, H-6b).

Anal. Calc. for $C_{31}H_{38}O_4$: C, 78.45; H, 8.07. Found: C, 78.38; H, 7.90.

(1R)-1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-D-(1²H)-arabino-hexitol (**22**). — The general procedure with **6** (69 mg, 0.1 mmol) and deuterium oxide (5 μL) gave, after column chromatography (4:1 hexane–ethyl acetate), **22** (29 mg, 70%), $[\alpha]_D^{22}$ +18° (*c* 1.58, chloroform); lit.[8] $[\alpha]_D$ +19°; ^{1}H-n.m.r.: δ 1.70 (ddd, 1 H, $J_{1,2a}$ 4.8, $J_{2a,3}$ 11.0, $J_{2a,2e}$ 13.0 Hz, H-2*a*), 2.07 (ddd, 1 H, $J_{1,2e}$ 1.7, $J_{2e,3}$ 5.0, $J_{2a,2e}$ 13.0 Hz, H-2*e*), 3.34 (ddd, 1 H, $J_{5,6}$ 3.0, $J_{5,6b}$ 4.3, $J_{4,5}$ 9.7 Hz, H-5), 3.49 (dd, 1 H, $J_{3,4}$ 8.7, $J_{4,5}$ 9.7 Hz, H-4), 3.62 (ddd, 1 H, $J_{2e,3}$ 5.0, $J_{3,4}$ 8.7, $J_{2a,3}$ 11.0 Hz, H-3), 3.68 (m, 2 H, H-6a,6b), and 3.98 (dd, 1 H, $J_{1,2e}$ 1.7, $J_{1,2a}$ 4.8 Hz, H-1).

Phenyl (3,4,6-tri-O-benzyl-2-deoxy-α-D-arabino-hexopyranosyl) ketone (**26**). — The general procedure with **6** (170 mg, 0.24 mmol) and benzaldehyde (37 μL, 0.36 mmol, 1.5 equiv.) gave phenyl-(3,4,6-tri-*O*-benzyl-2-deoxy-α-D-*arabino*-hexopyranosyl)methanol as a mixture of isomers (**23**; 81 mg, 65%), colorless syrup; ^{1}H-n.m.r. (selected data): (major isomer) δ 1.53 (ddd, 1 H, $J_{1,2}$ 5.0, $J_{2a,3}$ 8.6, $J_{2a,2b}$ 13.8 Hz, H-2a), 1.78 (dt, 1 H, $J_{1,2b} = J_{2b,3}$ 4.9, $J_{2a,2b}$ 13.8 Hz, H-2b), 3.18 (bs, 1 H, OH), 3.53 (t, 1 H, $J_{3,4} = J_{4,5}$ 7.0 Hz, H-4), 3.70 (dd, 1 H, $J_{5,6a}$ 3.6, $J_{6a,6b}$ 10.5 Hz, H-6a), 3.79 (dd, 1 H, $J_{5,6b}$ 6.0, $J_{6a,6b}$ 10.5 Hz, H-6b), 3.79 (m, 1 H, H-3), 3.87 [dt, 1 H, $J_{1,2a} = J_{1,2b}$ 5.0, $J_{1,CH(OH)}$ 9.3 Hz, H-1], 3.96 (ddd, 1 H, $J_{5,6a}$ 3.6, $J_{5,6b}$ 6.0, $J_{4,5}$ 7.0 Hz, H-5), and 4.71 [d, 1 H, $J_{1,CH(OH)}$ 9.3 Hz, C*H*(OH)]; (minor isomer) δ 1.46 (ddd, 1 H, $J_{1,2a}$ 3.9, $J_{2a,3}$ 5.5, $J_{2a,2b}$ 13.9 Hz, H-2a), 2.17 (ddd, 1 H, $J_{2b,3}$ 3.8, $J_{1,2b}$ 9.0, $J_{2a,2b}$ 13.9 Hz, H-2b), 2.57 (bs, 1 H, OH), 3.47 (t, 1 H, $J_{3,4} = J_{4,5}$ 4.6 Hz, H-4), 3.57 (dd, 1 H, $J_{5,6a}$ 4.3, $J_{6a,6b}$ 10.5 Hz, H-6a), 3.82 (dd, 1 H, $J_{5,6b}$ 6.6, $J_{6a,6b}$ 10.5 Hz, H-6b), 3.82 (m, 1 H, H-3), 4.02 [ddd, 1 H, $J_{1,2a}$ 3.9, $J_{1,CH(OH)}$ 4.9, $J_{1,2b}$ 9.0 Hz, H-1],

4.16 (m, 1 H, H-5), and 4.93 [d, 1 H, $J_{1,CH(OH)}$ 4.9 Hz, C*H*(OH)]; isomeric ratio, 3:1.

Oxidation of **23** (45 mg, 0.08 mmol) by use of the procedure for **11** gave, after column chromatography (3:1 hexane–ethyl acetate), **26** (31 mg, 69%), colorless syrup, $[\alpha]_D^{22}$ +63° (*c* 1.5, chloroform); ^{1}H-n.m.r.: δ 1.88 (ddd, 1 H, $J_{1,2a}$ 5.8, $J_{2a,3}$ 10.8, $J_{2a,2e}$ 13.0 Hz, H-2*a*), 2.78 (ddd, 1 H, $J_{1,2e}$ 2.1, $J_{2e,3}$ 4.9 $J_{2a,2e}$ 13.0 Hz, H-2*e*), 3.36 (ddd, 1 H, $J_{5,6a}$ 2.0, $J_{5,6b}$ 4.0, $J_{4,5}$ 8.9 Hz, H-5), 3.49 (dd, 1 H, $J_{5,6a}$ 2.0, $J_{6a,6b}$ 10.5 Hz, H-6a), 3.63 (t, 1 H, $J_{3,4} = J_{4,5}$ 8.9 Hz, H-4), 3.67 (dd, 1 H, $J_{5,6b}$ 4.0, $J_{6a,6b}$ 10.5 Hz, H-6b), 3.93 (ddd, 1 H, $J_{2e,3}$ 4.9, $J_{3,4}$ 8.9, $J_{2a,3}$ 10.8 Hz, H-3), and 5.19 (dd, 1 H, $J_{1,2e}$ 2.1, $J_{1,2a}$ 5.8 Hz, H-1).

Anal. Calc. for $C_{34}H_{34}O_5$: C, 78.14; H, 6.56. Found: C, 78.47; H, 6.58.

*1-(3,4,6-Tri-*O*-benzyl-2-deoxy-α-*D*-arabino-hexopyranosyl)-1-hexanone* (**27**). — The general procedure with **6** (133 mg, 0.19 mmol) and hexanal (34 μL, 0.28 mmol, 1.5 equiv.) gave, after column chromatography (17:3 toluene–ethyl acetate), 1-(3,4,6-tri-*O*-benzyl-2-deoxy-α-D-*arabino*-hexopyranosyl)-1-hexanol as a mixture of isomers (**24**; 72 mg, 74%), colorless syrup; ^{1}H-n.m.r. (selected data): (major isomer) δ 0.89 (t, 3 H, *J* 7.0 Hz, CH_3), 1.22–1.48 (m, 8 H, 4 CH_2), 1.74 (ddd, 1 H, $J_{1,2a}$ 3.9, $J_{2a,3}$ 7.1, $J_{2a,2b}$ 13.8 Hz, H-2a), 1.96 (ddd, 1 H, $J_{1,2b}$ 4.0, $J_{2b,3}$ 6.6, $J_{2a,2b}$ 13.8 Hz, H-2b), 3.50 (t, 1 H, $J_{3,4} = J_{4,5}$ 5.7 Hz, H-4), 3.63–3.80 (m, 5 H, H-1,3,6a,6b, C*H*OH) and 3.96 (ddd, 1 H, $J_{5,6a}$ 4.2, $J_{4,5}$ 5.7, $J_{5,6b}$ 6.1 Hz, H-5); (minor isomer) δ 1.65 (ddd, 1 H, $J_{1,2a}$ 3.2, $J_{2a,3}$ 5.7, $J_{2a,2b}$ 13.8 Hz, H-2a), and 2.19 (ddd, 1 H, *J* 3.9, 8.2 and 13.8 Hz, H-2b); isomeric ratio, 10:1.

Oxidation of **24** (31 mg, 0.06 mmol) by use of the procedure for **11** gave, after column chromatography (50:1 dichloromethane–ethyl acetate), **27** (23 mg, 73%), m.p. 67° (ethanol–water), $[\alpha]_D^{22}$ +17.5° (*c* 0.87, chloroform); ^{1}H-N.m.r.: δ 0.87 (t, 3 H, *J* 6.8 Hz, CH_3), 1.27 (m, 4 H, 2 CH_2), 1.56 (m, 2 H, CH_2), 1.75 (ddd, 1 H, $J_{1,2a}$ 5.8, $J_{2a,3}$ 10.2, $J_{2a,2e}$ 13.1 Hz, H-2*a*), 2.57 (t, 2 H, *J* 7.4 Hz, CH_2CO), 2.59 (ddd, 1 H, $J_{1,2e}$ 3.0, $J_{2e,3}$ 4.7, $J_{2a,2e}$ 13.1 Hz, H-2*e*), 3.49 (m, 2 H, H-4,5), 3.64 (ddd, 1 H, $J_{2e,3}$ 4.7, $J_{3,4}$ 8.3, $J_{2a,3}$ 10.2 Hz, H-3), 3.73 (m, 2 H, H-6a,6b), and 4.32 (dd, 1 H, $J_{1,2e}$ 3.0, $J_{1,2a}$ 5.8 Hz, H-1).

Anal. Calc. for $C_{33}H_{42}O_5$: C, 76.72; H, 7.80. Found: C, 76.92; H, 8.23.

*2-Methyl-1-(3,4,6-tri-*O*-benzyl-2-deoxy-α-*D*-arabino-hexopyranosyl)-1-propanone* (**28**). — The general procedure with **6** (155 mg, 0.22 mmol) and isobutyraldehyde (30 μL, 0.33 mmol, 1.5 equiv.) gave, after column chromatography (4:1 dichloromethane–ethyl acetate) 2-methyl-1-(3,4,6-tri-*O*-benzyl-2-deoxy-α-D-*arabino*-hexopyranosyl)-1-propanol as a mixture of isomers (**25**; 92 mg, 85%), colorless syrup; ^{1}H-n.m.r. (selected data): (major isomer) δ 0.88 (d, 3 H, *J* 6.7 Hz, CH_3), 0.98 (d, 3 H, *J* 6.7 Hz, CH_3), 1.70 (m, 1 H, $CHMe_2$), 1.71 (ddd, 1 H, $J_{1,2b}$ 4.0, $J_{2a,3}$ 6.5, $J_{2a,2b}$ 13.9 Hz, H-2a), 2.01 (ddd, 1 H, $J_{1,2b}$ 3.9, $J_{2b,3}$ 7.7, $J_{2a,2b}$ 13.9 Hz, H-2b), 2.43 (bs, 1 H, OH), 3.40 (m, 1 H, C*H*OH), 3.50 (t, 1 H, $J_{3,4} = J_{4,5}$ 5.3 Hz), 3.66 (dd, 1 H, $J_{5,6a}$ 4.2, $J_{6a,6b}$ 10.2 Hz, H-6a), 3.72–3.88 (m, 3 H, H-1,3,6b), and 3.99 (m, 1 H, H-5); (minor isomer) δ 1.71 (m, 1 H, H-2a) and 2.22 (ddd, 1 H, *J* 4.0, 8.0, and 13.8 Hz, H-2b); isomeric ratio, 10:1.

Oxidation of **25** (70 mg, 0.14 mmol) by use of the procedure for **11** gave, after

column chromatography (50:1 dichloromethane–ethyl acetate), **28** (62 mg, 89%), colorless syrup, $[\alpha]_D^{22}$ +9.5° (*c* 2.25, dichloromethane); ^{1}H-n.m.r.: δ 1.03 and 1.12 (2 d, 6 H, *J* 6.9 Hz, 2 CH_3), 1.77 (ddd, 1 H, $J_{1,2a}$ 5.9, $J_{2a,3}$ 10.3, $J_{2a,2e}$ 13.2 Hz, H-2*a*), 2.57 (ddd, 1 H, $J_{1,2e}$ 2.9, $J_{2e,3}$ 4.7, $J_{2a,2e}$ 13.2 Hz, H-2*e*), 3.12 (h, 1 H, *J* 6.9 Hz, C*H*Me_2), 3.46 (ddd, 1 H, $J_{5,6a}$ 2.8, $J_{5,6b}$ 3.9, $J_{4,5}$ 8.5 Hz, H-5), 3.52 (dd, 1 H, $J_{3,4}$ 7.6, $J_{4,5}$ 8.5 Hz, H-4), 3.67 (ddd, 1 H, $J_{2e,3}$ 4.7, $J_{3,4}$ 7.6, $J_{2a,3}$ 10.3 Hz, H-3), 3.73 (m, 2 H, H-6a,6b), and 4.52 (dd, 1 H, $J_{1,2e}$ 2.9, $J_{1,2a}$ 5.9 Hz, H-1).

Anal. Calc. for $C_{31}H_{36}O_5$: C, 76.20; H, 7.43. Found: C, 76.34; H, 7.57.

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EIN NEUER EFFIZIENTER WEG ZUR DARSTELLUNG VON GLYCOPYRANOSYLCYANIDEN (2,6-ANHYDROALDONONITRILEN) OHNE NACHBARGRUPPENBETEILIGUNG. REDUKTION VON 2,6-ANHYDRO-1-DESOXY-1-NITROALDITOLEN MIT PHOSPHORTRICHLORID

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ABSTRACT

D-Glucose, D-mannose, and D-galactose gave in two steps the corresponding per-*O*-acetyl-2,6-anhydro-1-deoxy-1-nitroheptitols. Treatment with phosphorus trichloride in pyridine gave directly the corresponding 3,4,5,7-tetra-*O*-acetyl-2,6-anhydroheptononitriles ("glycopyranosyl cyanides"). The same treatment was applied to the 3,4,5-tri-*O*-acetyl-2,6-anhydro-1-deoxy-1-nitrohexitols, prepared from D-xylose, D-lyxose, L-arabinose, and D-ribose, and led to the corresponding 3,4,5-tri-*O*-acetyl-2,6-anhydrohexononitriles in yields ranging from 65 to 80%. No anomerization was observed, thus allowing the preparation, in high yields, of cyanides having even the 1,2-*cis* configuration. The anhydronitriles were compared with other known examples of this class of compounds and conformational equilibria in solution determined by ^{1}H-n.m.r. spectroscopy. A significant anomeric effect of the cyano group is doubtful. Instead, a stabilizing effect by the 1,3-diaxial arrangement of a cyano group and an acetoxy substituent seems to be present.

ZUSAMMENFASSUNG

Durch Umsetzung der aus den Hexosen D-Glucose, D-Mannose und D-Galactose in zwei Schritten gut zugänglichen acetylierten 2,6-Anhydro-1-desoxy-1-nitro-heptitole mit PCl_3 in Pyridin lassen sich direkt die entsprechenden 3,4,5,7-Tetra-*O*-acetyl-2,6-anhydroheptononitrile ("Glycopyranosylcyanide") darstellen. Ebenso können die aus den Pentosen D-Xylose, D-Lyxose, L-Arabinose und D-Ribose erhältlichen Tri-*O*-acetyl-2,6-anhydro-1-desoxy-1-nitrohexitole in die 3,4,5-Tri-*O*-acetyl-2,6-anhydrohexononitrile übergeführt werden. Die Ausbeuten liegen zwischen 65 und 80%. Da die Reaktion nicht von Anomerisierungen begleitet wird, lassen sich somit auch *cis*-1,2-Cyanide in sehr guter Ausbeute gewinnen. Die dargestellten Anhydroaldononitrile wurden mit anderen bekannten Verbindungen dieser

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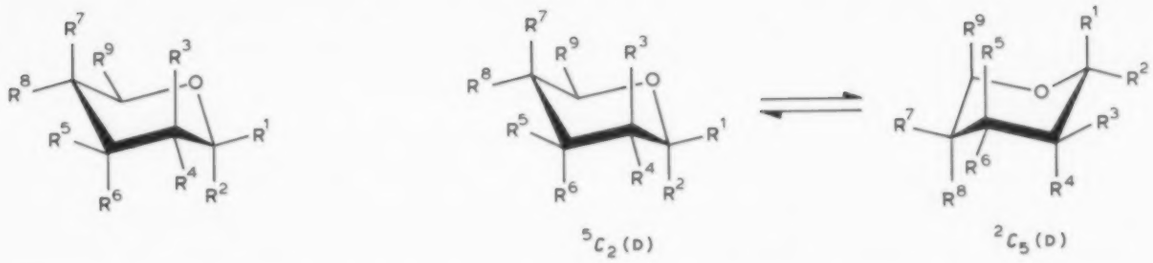
Klasse verglichen und insbesondere die Konformerengleichgewichte in Lösung durch ^{1}H-n.m.r.-Spektroskopie untersucht. Es ist zweifelhaft, ob die Cyanogruppe einen nennenswerten Anomeren Effekt ausübt, stattdessen scheint ein stabilisierender Effekt durch eine 1,3-diaxiale Anordnung einer Cyanogruppe und eines Acetylsubstituenten bewirkt zu werden.

EINLEITUNG

Glycosylcyanide stellen eine wichtige Klasse von *C*-Glycosyl Verbindungen dar, die einer Vielfalt weiterer Umsetzungen zugänglich sind[1]. Lange Zeit beschränkte sich das Interesse vorwiegend auf Furanosylcyanide (2,5-Anhydroaldononitrile) mit β-verknüpften Cyanofunktionen, da diese Verbindungen zur Synthese von *C*-Nucleosiden natürlicher Herkunft geeignet sind. Die entsprechenden pyranoiden Analoga (2,6-Anhydro-hexono- und -heptononitrile) wurden erst seit Beginn der siebziger Jahre intensiver untersucht.

Die genannten cyclischen Aldononitrile werden bisher überwiegend durch Cyanidisierungsreaktionen am anomeren Zentrum von entsprechend substituierten Furanosen und Pyranosen erhalten. Besonders durchgesetzt hat sich die Methode von Helferich *et al.*[2] (siehe auch Zit. 3–5), bei der ein Glycosylhalogenid mit Quecksilbercyanid entweder in der Schmelze oder in einem geeigneten Lösungsmittel wie Acetonitril oder auch Nitromethan behandelt wird. Zum anderen konnten dann in jüngerer Zeit de las Heras und Fernandes-Resa[6] sowie Utimoto und Horiie[7] zeigen, daß Trimethylsilylcyanid in Gegenwart einer Lewissäure zur Cyanidierung von 1-*O*-acylsubstituierten furanoiden oder pyranoiden Kohlenhydraten am anomeren Zentrum geeignet ist.

Beide Methoden haben jedoch gewichtige Nachteile. Die verwendeten Reagenzien sind nicht nur sehr toxisch, sondern es fallen auch cyanidhaltige Schwermetallabfälle an, die geordnet beseitigt werden müssen, was hohe Kosten verursacht. Daneben zeigen beide Methoden bei nachbargruppenaktiven Substituenten vicinal zum anomeren Zentrum eine hohe 1,2-*trans*-Stereoselektivität. Damit wird durch die Konfiguration an C-2 festgelegt, welches epimere Cyanid zugänglich ist. Das alternative Epimere fällt dabei jedoch meist zusätzlich in präparativ uninteressanten Mengen als Verunreinigung an. Werden dagegen Substituenten verwendet, die keinen solchen Einfluß ausüben, so wird unselektiv ein Gemisch der anomeren Glycosylcyanide erhalten. Bei der Quecksilbercyanid-Methode entstehen darüberhinaus noch die 1,2-*O*-(1-Cyanoalkyliden)-Produkte, wobei letztere häufig das Hauptprodukt stellen. Somit ist in den meisten Fällen eine chromatographische Trennung erforderlich. Aus diesen Gründen sind alternative Synthesemethoden von Interesse. Wir fanden, daß die Reduktion von 2,6-Anhydro-1-desoxy-1-nitroalditolen hier neue Wege eröffnet, obwohl auch dieses Verfahren nicht universell ist.



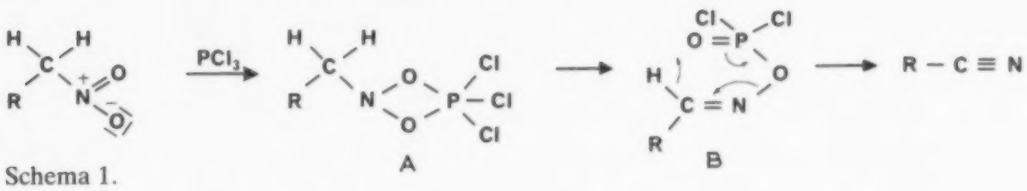
	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9
1	CH_2NO_2	H	H	OAc	OAc	H	H	OAc	CH_2OAc
2	CH_2NO_2	H	OAc	H	OAc	H	H	OAc	CH_2OAc
3	CH_2NO_2	H	H	OAc	OAc	H	OAc	H	CH_2OAc
4	CH_2NO_2	H	H	OAc	OAc	H	H	OAc	H
5	CH_2NO_2	H	OAc	H	OAc	H	H	OAc	H
6	CH_2NO_2	H	H	OAc	OAc	H	OAc	H	H
7	CH_2NO_2	H	H	OAc	H	OAc	H	OAc	H
8	H	CH_2NO_2	H	OAc	H	OAc	H	OAc	H
9	CN	H	H	OAc	OAc	H	H	OAc	CH_2OAc
10	CN	H	OAc	H	OAc	H	H	OAc	CH_2OAc
11	CN	H	H	OAc	OAc	H	OAc	H	CH_2OAc
12	CN	H	OAc	H	OAc	H	OAc	H	CH_2OAc
13	H	CN	OAc	H	H	OAc	H	OAc	CH_2OAc
14	H	CN	OAc	H	H	OAc	OAc	H	CH_2OAc
15	H	CN	H	OAc	OAc	H	H	OAc	CH_2OAc
16	H	CN	OAc	H	OAc	H	H	OAc	CH_2OAc
17	H	CN	H	OAc	OAc	H	OAc	H	CH_2OAc
18	CN	H	H	OAc	OAc	H	H	OAc	H
19	CN	H	OAc	H	OAc	H	H	OAc	H
20	CN	H	H	OAc	OAc	H	OAc	H	H
21	CN	H	H	OAc	H	OAc	H	OAc	H
22	H	CN	H	OAc	H	OAc	H	OAc	H

ERGEBNISSE UND DISKUSSION

Synthesen. — Durch Nitromethankondensation und anschließende Cyclisierung sind in einfacher Weise und in häufig sehr guter Ausbeute 2,6-Anhydro-1-desoxy-1-nitroalditole zugänglich[8–13]. In der Regel wird lediglich eines der möglichen Epimeren gebildet, und nur in seltenen Fällen wurden zusätzlich furanoide 2,5-Anhydride beobachtet[11,12,14]. Wir haben diese Reaktion umfassend untersucht und berichten über diese Ergebnisse an anderer Stelle[13]. So sind aus den Aldohexosen D-Glucose, D-Mannose und D-Galactose die acetylierten Nitroalditole **1, 2** und **3** direkt in zwei Schritten erhältlich. Die Pentosen D-Xylose, D-Lyxose und L-Arabinose liefern entsprechend die Verbindungen **4, 5** und **6**. Lediglich D-Ribose gibt[13] auf diese Weise ein Isomerengemisch von **7** und **8**. Derartige acylierte Anhydronitroalditole sind hervorragende Edukte, um sie nach der von Wehrli und Schaer[15] für aliphatische und aromatische Nitroverbindungen beschriebenen Methode mit Phosphortrichlorid zu den Nitrilen zu reduzieren. Die Umsetzung

erfolgt mit 1.1 mol Phosphortrichlorid in Pyridin bei Raumtemperatur. So erhält man aus **1** das β-D-Glucopyranosylcyanid[5] **9**, aus **2** das β-D-Mannopyranosylcyanid[5] **10** und aus **3** das β-D-Galactopyranosylcyanid[5] **11**. Die sich von den Pentosen ableitenden Nitroverbindungen **4, 5, 6** sowie **7** und **8** liefern entsprechend das β-D-Xylopyranosylcyanid[3] **18**, das β-D-Lyxocyanid **19**, das α-L-Arabinocyanid[3] **20**, sowie das β-D-Ribocyanid[6] **21** und das α-D-Ribocyanid **22**. Die Ausbeuten liegen zwischen 65 und 80%, wobei die meisten Produkte direkt kristallisieren. Nebenprodukte werden nicht beobachtet.

Obwohl keine Untersuchungen zum Reaktionsmechanismus vorliegen, werden einige plausible Reaktionsschritte diskutiert[15]. Der Angriff von P(III) am Sauerstoffatom der Nitrogruppe kann zu einem cyclischen Zwischenprodukt **A** führen, wobei das Stickstoffatom formal auf die Nitrososstufe reduziert wird. Die Abspaltung von Hydrogenchlorid ergibt einen Oximphosphatester **B**, der nachfolgend sofort weiter Phosphorsäure-dichlorid zum Nitril eliminiert (Schema 1).



Schema 1.

Die Reaktionsprodukte zeichnen sich durch das Fehlen der Nitro-Bande bei 1540–1570 cm^{-1} im i.r.-Spektrum aus. Erwartungsgemäß wird aber auch keine Nitril-Bande beobachtet[16]. Sehr leicht können die Reaktionsprodukte als Cyanide jedoch aufgrund ihrer ^{13}C-n.m.r.-Spektren erkannt werden, soweit nicht ein Vergleich mit bereits publizierten anderen physikalischen Daten beschriebener Verbindungen zu einer eindeutigen Produktidentifizierung führt. Man findet ein Signal bei δ ~116, das eindeutig dem Cyanokohlenstoffatom in den Glycopyranosylcyaniden zuzuordnen ist (vergl. Tabelle I). Die Konfiguration an C-2 ergibt sich allerdings aus diesen Spektren nicht in einfacher Weise. Hier können die ^1H-n.m.r.-Spektren (vergl. Tabelle II) helfen, die nicht nur die Aufklärung der Stereochemie an diesem Chiralitätszentrum erlauben, sondern darüberhinaus wertvolle Aussagen über Vorzugskonformationen in Lösung liefern (s.u.). In allen von uns untersuchten Fällen bleibt die Konfiguration an C-2, die in der Ausgangsnitroverbindung vorlag, bei der Reduktion zum Cyanid erhalten.

Die direkte Umwandlung von 2,6-Anhydro-1-desoxy-1-nitroalditolen in die entsprechenden Glycopyranosylcyanide muß somit als interessante Ergänzung der bereits bekannten Cyanidierungsmethoden von Kohlenhydraten angesehen werden. Es treten nicht nur keine Nebenprodukte auf, so daß auf chromatographische Trennung verzichtet werden kann, sondern es ist auch möglich bei Vorliegen geeigneter Edukte sogar 1,2-*cis*-Cyanide, wie z.B. **10, 19** und **22**, in hoher Ausbeute zu erhalten, was die anderen bisher bekannten Verfahren ausschließen. Zu Vergleichszwecken wurden im Zusammenhang mit dieser Arbeit nach der Tri-

TABELLE I

^{13}C-N.M.R.-SIGNALE[a] (δ) DARGESTELLTER 2,6-ANHYDROALDONONITRILE **9–11, 13**

Verbindung	*CN*	*C-2 bis C-6*	*C-7*
9	115.9	77.0; 73.3; 69.8; 68.4; 66.4	62.4
10	115.5	77.2; 71.1; 68.9; 67.2; 65.9	62.8
11	116.2	76.1; 71.4; 68.2; 67.1; 66.9	62.3
13	115.6	70.6; 69.4; 66.7; 65.2; 64.4	62.7
14	116.0	70.5; 66.7; 66.1; 65.6; 64.9	62.9
18	116.1	71.2; 69.3; 68.8; 65.5(2)	
19	116.1	68.0; 67.6; 66.7; 65.2; 65.1	
20	116.3	70.3; 68.2; 67.7(2); 66.8	
21	116.5	68.5; 67.3; 66.4; 64.8; 64.7	
22	116.4	67.4; 66.6; 66.3; 64.3; 63.3	

[a]Me_4Si interner Standard; alle Messungen bei 20.1 MHz für ($^2H_6$)Acetonlösun

1, 13, 14, 18–22

	C=O	CH_3	*Anmerkung*
	170.8; 170.3; 169.6; 169.6	20.4(3); 20.3	vergl. Zit. 5
	170.8(2); 170.2(2)	20.5(2); 20.4(2)	vergl. Zit. 5
	170.7(2); 170.2; 169.7	20.4	vergl. Zit. 5
	170.7; 169.9; 169.8; 169.6	20.5	
	170.8; 170.3; 169.8; 169.1	20.7; 20.6(3)	
	170.1(2); 169.6	20.5(2); 20.3	vergl. Zit. 18
	170.2(2); 170.1	20.6(2); 20.3	
	170.5(2); 170.2	20.7; 20.6(2)	D-Enantiomer Zit. 18
	170.0; 169.6(2)	20.4	vergl. Zit. 6
	170.2(2); 169.8	20.5; 20.3(2)	

ösungen.

TABELLE II

^{1}H-N.M.R.-SIGNALE (δ) VON 2,6-ANHYDRO-ALDONONITRILEN[a]

Verbindung	*Lösungs-mittel*	*H-2*	*H-3*	*H-4*	*H-5*	
9	$CDCl_3$	4.33(d) $J_{2,3}$ 10.1	5.32(t) $J_{3,4}$ 9.3	5.18(t) $J_{4,5}$ 9.3	5.11(t) $J_{5,6}$ 9.6	3 J J
	C_6D_6	3.49(d) $J_{2,3}$ 9.7	5.4–4.9(m)		 $J_{5,6}$ 10.5	3 J J
10	$CDCl_3$	4.59(d) $J_{2,3}$ 1.4	5.62(dd) $J_{3,4}$ 3.4	5.05(dd) $J_{4,5}$ 10.0	5.26(t) $J_{5,6}$ 9.9	3 J J
	C_6D_6	3.35(d) $J_{2,3}$ 1.4	5.44(dd) $J_{3,4}$ 3.4	4.89(dd) $J_{4,5}$ 10.2	5.46(t) $J_{5,6}$ 9.9	3 J J
11	$CDCl_3$	4.30(d) $J_{2,3}$ 10.1	5.54(t) $J_{3,4}$ 10.2	5.01(dd) $J_{4,5}$ 3.3	5.44(dd) $J_{5,6}$ 1.1	3 J J
	C_6D_6	3.99(d) $J_{2,3}$ 10.2	5.66(t) $J_{3,4}$ 10.2	5.01(dd) $J_{4,5}$ 3.3	5.41(dd) $J_{5,6}$ 1.2	3 J J
12	$CDCl_3$	4.66(d) $J_{2,3}$ 1.6	5.49(bs) $J_{3,4}$ 3.7	5.12(t) $J_{4,5}$ 3.7	5.32(d) $J_{5,6}$ 1.6	3 J J
13	$CDCl_3$	4.81(dd) $J_{2,3}$ 1.4; $J_{2,4}$ 0.8	5.00(dd) $J_{3,4}$ 3.7	5.31(dt) $J_{4,5}$ 3.0	5.11(dd) $J_{5,6}$ 9.2	4
	C_6D_6	4.36(bs) $J_{2,3}$ 1.5	4.99(dd) $J_{3,4}$ 3.7	5.59(dt) $J_{4,5}$ 3.1	5.36(dd) $J_{5,6}$ 9.7	3

H-6	*H-6'*	*H-7*	*H-7'*	*OAc*	*Zit.*
3.72(ddd) $J_{6,7}$ 4.8; $J_{6,7'}$ 2.3		4.24(dd) $J_{7,7'}$ 12.8	4.15(dd)	2.03; 2.04; 2.11(6H)	5
3.00(m) $J_{6,7}$ 5.0; $J_{6,7'}$ 2.4		4.14(dd) $J_{7,7'}$ 12.0	3.88(dd)	1.64(9H); 1.70	
3.70(ddd) $J_{6,7}$ 5.7; $J_{6,7'}$ 2.4		4.26(dd) $J_{7,7'}$ 12.6	4.17(dd)	2.00; 2.06 2.12; 2.26	5
3.09(ddd) $J_{6,7}$ 4.8; $J_{6,7'}$ 2.5		4.25(dd) $J_{7,7'}$ 12.5	3.96(dd)	1.64; 1.65; 1.69; 1.70	
3.95(dt) $J_{6,7}$ 6.4; $J_{6,7'}$ 6.4		4.1(m)		2.01; 2.07 2.13; 2.20	5
3.63(dt) $J_{6,7}$ 6.8; $J_{6,7'}$ 6.8		4.0(m)		1.68(6H); 1.73; 1.74	
3.97(bt) $J_{6,7}$ 6.2; $J_{6,7'}$ 6.2		4.2(m)		2.01; 2.08; 2.16; 2.23	17
4.1–4.5(mb)		4.1–4.5(m)		1.99; 2.04; 2.13; 2.15	
3.9–4.5(m)		3.9–4.5(m)		1.40; 1.65(6H); 1.83	

14	$CDCl_3$	4.90(m)		5.05(m)	4.9(m) $J_{5,6}$ 1.4
	C_6D_6	4.40(ds) $J_{2,3}$ 1.8; $J_{2,4}$ 1	4.9(m) $J_{3,4}$ 3.4	5.20(dt) $J_{4,5}$ 3.4	4.9(m) $J_{5,6}$ 2.0
15	$CDCl_3$	5.14(d) $J_{2,3}$ 6.2	5.03(dd) $J_{3,4}$ 9.8	5.46(t) $J_{4,5}$ 9.6	5.09(t) $J_{5,6}$ 9.8
16	$CDCl_3$	4.91(d) $J_{2,3}$ 2.0	5.43(dd) $J_{3,4}$ 3.0	5.37(dd) $J_{4,5}$ 9.5	5.31(t) $J_{5,6}$ 9.4
17	$CDCl_3$	5.18(d) $J_{2,3}$ 5.6	5.25(dd) $J_{3,4}$ 10.6	5.31(dd) $J_{4,5}$ 2.9	5.53(dd) $J_{5,6}$ 1.1
18	$CDCl_3$	4.50(d)	5.0–5.2(m)		4.92(m) $J_{5,6}$ 4.0; $J_{5,6'}$ 7.0
	C_6D_6	3.66(d) $J_{2,3}$ 8.0	5.0–5.2(m)		4.75(m) $J_{5,6}$ 4.4; $J_{5,6'}$ 8.0
19	$CDCl_3$	4.83(d)	5.2–5.4(m)		5.01(m) $J_{5,6}$ 2.2; $J_{5,6'}$ 3.3
	C_6D_6	3.92(d) $J_{2,3}$ 4.8	5.2–5.4(m)	$J_{4,5}$ 5.2	4.88(m) $J_{5,6}$ 2.8; $J_{5,6'}$ 4.4
20	$CDCl_3$	4.49(d) $J_{2,3}$ 5.9	5.1–5.4(m)		$J_{5,6}$ 5.8; $J_{5,6'}$ 3.6
	C_6D_6	3.65(d) $J_{2,3}$ 7.2	5.46(t) $J_{3,4}$ 7.2	4.96(dd) $J_{4,5}$ 3.2	5.10(ddd) $J_{5,6}$ 4.7; $J_{5,6'}$ 2.6

4.75(ddd) $J_{6,7}$ 7.0; $J_{6,7'}$ 5.0		4.1–4.3(m)		2.11; 2.16(6H); 2.21	
4.45(ddd) $J_{6,7}$ 6.8; $J_{6,7'}$ 5.6		4.0–4.2(m) $J_{7,7'}$ 13.0		1.40; 1.55; 1.59; 1.64	
4.11(ddd) $J_{6,7}$ 4.3; $J_{6,7'}$ 2.2		4.32(dd) $J_{7,7'}$ 12.7	4.16(dd)	2.05; 2.06; 2.10; 2.14	5
4.09(dd) $J_{6,7}$ 2.3; $J_{6,7'}$ 5.3		4.32(dd) $J_{7,7'}$ 12.6	4.17(dd)	2.03; 2.08; 2.12; 2.20	5
4.31(dt) $J_{6,7}$ 6.3; $J_{6,7'}$ 6.3		4.13(m)		2.02; 2.07; 2.15	5
4.24(dd) $J_{6,6'}$ 12.5	3.60(dd)			2.10; 2.15	vergl. 18
3.74(dd) $J_{6,6'}$ 12.1	2.83(dd)			1.57; 1.61; 1.68	
4.25(dd) $J_{6,6'}$ 13.2	3.81(dd)			2.16; 2.21(6H)	
3.90(dd) $J_{6,6'}$ 13.0	3.28(dd)			1.54; 1.65; 1.84	
4.11(dd) $J_{6,6'}$ 12.5	3.75(dd)			2.15	vergl. 18
3.58(dd) $J_{6,6'}$ 12.6	2.86(dd)			1.56(6H); 1.72	

TABELLE II *(Fortsetzung)*

Verbindung	*Lösungs-mittel*	*H-2*	*H-3*	*H-4*	*H-5*
21	$CDCl_3$	4.56(d) $J_{2,3}$ 8.8	5.13(dd) $J_{3,4}$ 2.9	5.62(bt) $J_{4,5}$ 2.9	5.07(ddd) $J_{5,6}$ 4.9; $J_{5,6'}$ 9.0
	C_6D_6	4.03(d) $J_{2,3}$ 9.0	5.03(dd) $J_{3,4}$ 2.8	5.65(dt) $J_{4,5}$ 2.9; $J_{4,6}$ 0.6	4.73(ddd) $J_{5,6}$ 5.0; $J_{5,6'}$ 9.3
22	$CDCl_3$	4.86(d) $J_{2,3}$ 5.9	5.08(dd) $J_{3,4}$ 2.8	5.61(bt) $J_{4,5}$ 2.8	5.02(ddd) $J_{5,6}$ 9.0; $J_{5,6'}$ 6.0
	C_6D_6	4.22(d) $J_{2,3}$ 5.9	5.73(dd) $J_{3,4}$ 2.8	5.30(bt) $J_{4,5}$ 2.8; $J_{4,6}$ 0.8	4.78(ddd) $J_{5,6}$ 9.6; $J_{5,6'}$ 5.0

[a] Me_4Si als innerer Standard und Kopplungskonstanten J in Hz.

	H-6	*H-6'*	*H-7*	*H-7'*	*OAc*	*Zit.*
)	3.99(dd) $J_{6,6'}$ 11.5	3.56(dd)			2.04; 2.10 2.15	6
)	3.56(ddd) $J_{6,6'}$ 11.5	3.19(dd)			1.53; 1.58; 1.65	
)	4.04(dd) $J_{6,6'}$ 11.5	3.85(dd)			2.11; 2.15; 2.24	
)	3.88(dd) $J_{6,6'}$ 11.4	3.46(ddd)			1.63; 1.68; 1.95	

methylsilylcyanidmethode[6] die bisher nicht beschriebenen α-D-Cyanide **13** und **14** der D-Altro- und der D-Idopyranose dargestellt.

Konformation von Glycopyranosylcyaniden. — Die bekannten und in der vorliegenden Arbeit erstmals beschriebenen 2,6-Anhydroaldononitrile ermöglichen eine umfassende Untersuchung der in Lösung eingenommenen Vorzugskonformationen anhand der ^{1}H-n.m.r.-Daten (vergl. Tabelle II). Interessant ist in diesem Zusammenhang die Frage, ob die Cyanogruppe als Pseudohalogenid evtl. einen Anomeren Effekt[19] zeigt. Da in derartigen Fällen häufig ein starker Lösungsmitteleinfluß beobachtet werden kann, wurden die Spektren sowohl in (^{2}H)-Chloroform- als auch ($^2H_6$)Benzollösungen aufgenommen.

2,6-Anhydroheptononitrile. Die Hydroxymethylgruppe bevorzugt in den Hexopyranosen aus sterischen Gründen meist die equatoriale Position, so daß diese meist in der $^4C_1$(D)-Konformation vorliegen[20]. Gleiche Verhältnisse sind auch bei den untersuchten β-D-Glycopyranosylcyaniden gegeben. Hier finden sich sowohl die Cyano- als auch die Hydroxymethylgruppe in equatorialer Position, wenn die Verbindung eine $^5C_2$(D)-Konformation einnimmt. Im *gluco*-Isomer **9** bedeutet dies eine all-equatoriale Anordnung der Substituenten. Die Kopplungskonstanten der Ringprotonen zeigen entsprechend Werte um 10 Hz. Im *galacto*-Isomer **11** werden ebenfalls Kopplungskonstanten gefunden, die mit der $^5C_2$(D)-Konformation übereinstimmen ($J_{2,3} = J_{3,4}$ 10 Hz; $J_{5,6}$ 1.2 Hz). Das gleiche gilt auch für das β-D-*manno*-Cyanid **10** ($J_{2,3}$ 1.4 Hz; $J_{4,5} = J_{5,6}$ 10 Hz). Probleme bereitet lediglich die β-D-*talo*-Verbindung **12**, deren ^{1}H-n.m.r.-Spektrum in der Literatur beschrieben wurde[17]. Wie der Tabelle II zu entnehmen ist, zeigen β-D-Hexopyranosylcyanide eine Chemische Verschiebung für das anomere Proton, die im Bereich von δ 4.3–4.6 ($CDCl_3$) liegt. Für **12** wurde aber δ 5.32 angegeben. Auch die entsprechende Kopplungskonstante $J_{2,3}$ 3.7 Hz erscheint mit der vorliegenden Konfiguration unvereinbar. Im β-D-*manno*-Isomer **10**, das an C-2 und C-3 die gleiche Konfiguration besitzt, wird nur eine Kopplungskonstante $J_{2,3}$ 1.4 Hz beobachtet. Diese Überlegungen führten dazu, daß die Interpretation des Spektrums korrigiert werden muß. Die in Tabelle II enthaltene Neuzuordnung der Meßdaten[17] erklärt zwanglos auch für **12** eine $^5C_2$(D)-Konformation. Die möglicherweise im berichteten Signal δ 5.49 (bs) enthaltene Fernkopplung $J_{3,5}$ wäre hiermit gleichermaßen sehr gut vereinbar.

In den sich von D-Glucose, D-Mannose und D-Galactose ableitenden α-Cyaniden[5] **15, 16** und **17** werden Kopplungskonstanten gefunden, die ebenfalls mit einer equatorialen Anordnung der Acetoxymethylgruppe, und in diesen Fällen, axialen des Cyanosubstituenten vereinbar sind. Auch diese Verbindungen liegen also in der $^5C_2$(D)-Konformation vor. Auffallend ist allerdings die große Kopplungskonstante $J_{2,3}$ von 6.2 bzw. 5.6 Hz in den Cyaniden **15** und **17** mit *e,a*-Anordnung der Substituenten in 2,3-Stellung, die aber bei Berücksichtigung elektronischer Effekte verständlich sein sollte[21]. Das *altro*-Isomer **13** zeigt Kopplungskonstanten von $J_{5,6}$ 9.7, $J_{2,3}$ 1.4 und $J_{2,4}$ 0.8 Hz, ebenfalls in Einklang mit vorgenannter Konformation. Auch die für **14** gemessenen Spektrenparameter stehen in

guter Übereinstimmung mit α-D-*ido*-Derivativen, die aufgrund von *O*-1-Substituenten mit starkem Anomeren Effekt ausschließlich in der $^4C_1$(D)-Konformation auftreten[22]. Somit liegt auch **14** hauptsächlich in der analogen $^5C_2$(D)-Konformation vor. Die Untersuchungen aus der Idose-Reihe[22], wo bei Substituenten mit schwachem Anomeren Effekt ein Gleichgewicht der alternativen Sesselkonformationen $^1C_4$(D) und $^4C_1$(D) gefunden wird, wobei $^1C_4$(D) sogar häufig überwiegt, lassen insbesondere aufgrund der für **14** gemessenen Daten einen ausgeprägten Anomeren Effekt[19] der Cyanogruppe vermuten. Alternativ muß jedoch auch eine Stabilisierung der $^5C_2$(D)-Konformation in **14** über günstige Wechselwirkungen zwischen der axialen Cyanogruppe und einer axialen Acetylgruppe in 3-Stellung diskutiert werden (s.u.).

2,6-Anhydrohexononitrile. Diesen Verbindungen fehlt der konformationsstabiliserende Einfluß der Acetoxymethylgruppe. Somit ist hier eine höhere konformative Flexibilität zu erwarten und der Einfluß der Cyanogruppe auf die Konformation sollte stärker zutage treten als bei den vorstehend behandelten Heptononitrilen. Alle bekannten Verbindungen dieser Klasse wurden in die Untersuchungen einbezogen.

Das konformative Gleichgewicht wurde aus den Kopplungskonstanten $J_{2,3}$ in üblicher Weise berechnet[23]. Es wurde lediglich ein Gleichgewicht der alternativen Sesselkonformationen $^2C_5$(D) und $^5C_2$(D) zugrunde gelegt. Andere Konformere wurden bei diesen Überlegungen nicht berücksichtigt. Die idealen Kopplungskonstanten wurden aus den 2,6-Anhydroheptononitrilen **9–17** abgeleitet. Dabei wurden folgende Werte ausgewählt: $J_{e,e}$ 1.4 Hz (aus **13**); $J_{a,a}$ 10 Hz (aus **9** und **11**); $J_{e,a}$ 6.2 Hz (aus **15**) und $J_{a,e}$ 1.4 Hz (aus **10**). Die Ergebnisse dieser Berechnungen finden sich in Tabelle III. Alle weiteren auftretenden Kopplungskonstanten können zwanglos ebenfalls mit diesen Konformationsgleichgewichten erklärt werden. Nur im Falle des α-L-Arabinopyranosylcyanides **20** findet sich eine signifikante Abhängigkeit des Konformerengleichgewichtes von den verwendeten

TABELLE III

KONFORMERENGLEICHGEWICHTE DER 2,6-ANHYDROHEXONONITRILE

Verbindung (Konfigurations bezeichnungen beziehen sich auf Glycosylcyanidnomenklatur)		*Konformer (%)*		*Lösungsmittel*
		$^5C_2$(D)	$^2C_5$(D)	
β-D-*xylo*	(**18**)	77	23	C_6D_6
β-D-*lyxo*	(**19**)	29	71	C_6D_6
β-D-*ribo*	(**21**)	89	11	C_6D_6
α-D-*ribo*	(**22**)	94	6	C_6D_6
α-D-*arabino*[18]		43	57	$CDCl_3$
		$^2C_5$(L)	$^5C_2$(L)	
α-L-*arabino*	(**20**)	48	52	$CDCl_3$
α-L-*arabino*	(**20**)	33	67	C_6D_6

Lösungsmitteln. Alle anderen Beispiele zeigen annähernd die gleichen Kopplungskonstanten und damit die gleichen Konformeren gleichgewichte in (^{2}H)Chloroform und ($^2H_6$)Benzol. Für das Benzoylanalogon des β-D-Ribocyanids **21** wurde jedoch ebenfalls eine gewisse Lösungsmittelabhängigkeit der Konformerengleichgewichte berichtet[24].

Auch hier fällt es schwer, Aussagen über einen möglichen Anomeren Effekt[19] der Cyanogruppe zu machen, bzw. dessen Größe abzuschätzen. Auffällig ist aber, daß Konformationen mit einer 1,3-diaxialen Wechselwirkung zwischen einer Acetoxygruppe und einer Cyanogruppe scheinbar bevorzugt werden. So liegen **22** ("α-D-*ribo*") und **19** ("β-D-*lyxo*"), wie auch schon die Derivative **13** und **14**, überwiegend in derjenigen Konformation vor, die diese 1,3-diaxiale Wechselwirkungen erlaubt. Noch deutlicher tritt der mögliche stabilisierende Einfluß einer 1,3-diaxialen Wechselwirkung zwischen OAc und CN im Vergleich der β-D-*xylo*- und β-D-*ribo*-Derivative **18** und **21** zutage. Verbindung **21** kann in keiner Konformation 1,3-diaxiale Wechselwirkungen zwischen OAc und CN ausbilden. Dagegen ist **18** in der $^2C_5$(D)-Konformation dazu befähigt. Die $^5C_2$(D)-Konformation von **18** führt demgegenüber zu einer all-equatorialen Anordnung der großen Substituenten, und sollte somit die energetisch weitaus günstigste Anordnung darstellen. Dennoch findet man ein Konformerenverhältnis $^5C_2$(D) zu $^2C_5$(D) von 4:1 in **18**. Dieses Ergebnis könnte durch einen starken Anomeren Effekt in der Größenordnung der Acetoxygruppe erklärt werden, der die all-axiale $^2C_5$(D)-Konformation stabilisiert, wie dies bei 1,2,3,4-Tetra-*O*-acetyl-β-D-xylopyranose[21,24] ($^4C_1$:$^1C_4$ = 7:3) beobachtet wird. Hat die Cyanogruppe tatsächlich jedoch einen Anomeren Effekt, der in der Größenordnung dessen der Acetoxygruppe liegt, so sollte man im β-D-*ribo*-Derivat **21** eine ähnliche Konformerenverteilung wie bei 1,2,3,4-Tetra-*O*-acetyl-β-D-ribopyranose ($^4C_1$:$^1C_4$ = 2:3) erwarten[25]. Dies ist jedoch nicht der Fall. Man findet stattdessen ein Verhältnis von 9:1 zugunsten der $^5C_2$(D)-Konformation. Dies bedeutet aber, daß die Cyanogruppe keinen Anomeren Effekt besitzt, dessen Größe dem der Acetoxygruppe auch nur annähernd gleichkommt. Stattdessen scheinen mögliche *syn*-diaxiale Anordnungen von anomerer Cyanogruppe und Acetoxysubstituent in 3-Stellung gleichgewichtsbestimmend zu sein.

Über die Art einer Stabilisierung, die eine Konformation mit 1,3-diaxialen Wechselwirkung zwischen einer Acetoxy- und Cyanogruppe eventuell erfahren kann, kann nur spekuliert werden. Vielleicht spielen elektronische Effekte eine Rolle und es bildet sich ein Charge–Transfer-Komplex zwischen dem Nitril und der Acetoxygruppe aus. Hinweise dazu liefert ebenfalls das ^{1}H-n.m.r.-Spektrum dieser Verbindungen. Eine Übertragung von Elektronendichte der Carbonylgruppe auf die Nitrilgruppe müßte zu einer relativen Positivierung des Carbonylkohlenstoffatoms führen. Dieser Effekt könnte an einer geringen Tieffeldverschiebung der Acetatmethylgruppe im ^{1}H-n.m.r.-Spektrum beobachtet werden. Die Ausbildung eines Acetoxoniumions führt z.B. zu einer Tieffeldverschiebung des Methylsignals um ~1 p.p.m. Bei **22** und **19** findet man die Tieffeldverschiebung eines Acetyl-

signales um ~0.2 p.p.m. auf δ 1.95 bzw. 1.84 für eine Lösung in ($^2H_6$)Benzol. Ein ähnlicher Effekt tritt bei **13** auf. Nur im D-*ido*-Derivat **14** ist dies nicht zu beobachten. Diese geringe Tieffeldverschiebung könnte tatsächlich durch einen Charge–Transfer-Komplex zwischen einer Carbonyloxygruppe und einer Cyanogruppe verursacht werden. Derartige Effekte wurden auch bereits früher in anderen Fällen diskutiert[25].

Berechnet man die sterischen Effekte in den alternativen Sesselkonformationen unter Zugrundelegung eines üblicherweise benutzten Parametersatzes[23] und führt lediglich einen neuen Energieterm für eine 1,3-diaxiale Wechselwirkung zwischen CN und H von 1.3 kJ/mol ein, errechnet sich eine Stabilisierungsenergie in der Größenordnung von 4 kJ/mol. Sie ist bei Abschätzung der Konformerengleichgewichte von **18, 19, 20** und **22** zu berücksichtigen, nicht jedoch bei **21**. Natürlich ist das vorhandene Datenmaterial zu dürftig, um eine solche Hypothese belegen zu können, doch scheint es sinnvoll, diesem Effekt weitere Untersuchungen zu widmen.

EXPERIMENTELLER TEIL

Allgemeine Methoden. — Die angegebenen Schmp. sind nicht korrigiert. Drehwerte wurden in einer 10 cm-Küvette mit einem Perkin–Elmer-Polarimeter Modell 241 MC bestimmt und n.m.r.-Spektren mit einem Bruker WP 80 Spektrometer. Alle Reaktionen wurden dünnschichtchromatographisch an Kieselgel (Merck) verfolgt. Säulenchromatographie: Kieselgel 60 (Merck).

Allgemeine Arbeitsvorschrift (AAV) (A). — Vollständig acetyliertes 2,6-Anhydro-1-desoxy-1-nitroalditol (1 mmol) wird in abs. Pyridin (3 mL) gelöst, im Eisbad gekühlt und in der Kälte mit PCl_3 (1.1 mmol) versetzt und dann 16 h bei Raumtemperatur gerührt. Die Lösung wird auf eisgekühlte M HCl (20 mL) gegossen, 20 min gerührt und dreimal (je 10 mL) mit Chloroform extrahiert. Die organische Phase wird zweimal mit $NaHCO_3$-Lösung, dann mit Wasser gewaschen. Nach Trocknen der organischen Phase ($MgSO_4$) und Einengen erhält man das reine Glycosylcyanid.

Allgemeine Arbeitsvorschrift (AAV) (B). — Die Vorschrift von de las Heras und Fernandes-Resa[6] zur Cyanidierung von Kohlenhydraten mit Trimethylsilylcyanid[26] (Me_3SiCN) wurde unter folgenden Modifikationen übernommen: (a) Es wurde unter Inertgasatmosphäre gearbeitet. (b) Nach 24 h Rühren wurde weiteres Me_3SiCN und $BF_3 \cdot OEt_2$ zugesetzt und weitere 16–18 h gerührt. Aufarbeitung erfolgte wie beschrieben[6].

3,4,5,7-Tetra-O-*acetyl-2,6-anhydro*-D-glycero-D-gulo-*heptononitril* (**9**). — (*a*). Umsetzung von 1,2,3,4,6-Penta-*O*-acetyl-α-D-glucopyranose (1 g, 2.56 mmol; Sigma Katalog-Nr. G-5125) gemäß AAV (*B*) führt zu Cyanid **9** (0.40 g, 45%). (*b*). Umsetzung von 1,2,3,4,6-Penta-*O*-acetyl-β-D-glucopyranose (1 g, 2.56 mmol; Sigma Katalog-Nr. G-5175) gemäß AAV (*B*) führt zu Cyanid **9** (0.36 g, 40%). (*c*) 3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-desoxy-1-nitro-D-*glycero*-D-*gulo*-heptitol[27]

(0.39 g, 1 mmol) wird gemäß AAV (*A*) umgesetzt und führt zu Cyanid **9** (0.26 g, 73%), Schmp. 113–114°, $[\alpha]_D^{20}$ +9.4° (*c* 0.9, Chloroform); Lit.[5] Schmp. 114–115°, $[\alpha]_D^{20}$ +10.7° (*c* 3.3, Chloroform).

Anal. Ber. für $C_{15}H_{19}NO_9$ (357.3): C, 50.42; H, 5.36; N, 3.92. Gef.: C, 50.52; H, 5.39; N, 3.79.

3,4,5,7-Tetra-O-*acetyl-2,6-anhydro*-D-glycero-D-galacto-*heptononitril* (**10**). — 3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-desoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol[28] (0.39 g, 1 mmol) wird gemäß AAV (*A*) umgesetzt und führt zu Cyanid **10** (0.23 g, 64%), Schmp. 141–142°, $[\alpha]_D^{20}$ −20.4° (*c* 0.8, Chloroform); Lit.[5] Schmp. 143–144°, $[\alpha]_D^{20}$ −20.9° (*c* 3.8, Chloroform).

Anal. Ber. für $C_{15}H_{19}NO_9$ (357.3): C, 50.42; H, 5.36; N, 3.92. Gef.: C, 50.35; H, 5.34; N, 3.89.

3,4,5,7-Tetra-O-*acetyl-2,6-anhydro*-D-glycero-L-manno-*heptononitril* (**11**). — 3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-desoxy-1-nitro-D-*glycero*-L-*manno*-heptitol[11] (0.39 g, 1 mmol) wird gemäß AAV (*A*) umgesetzt und führt zu Cyanid **11** (0.28 g, 78%), Schmp. 167–168°, $[\alpha]_D^{20}$ +32.1° (*c* 1.4, Chloroform); Lit.[5] Schmp. 167–168°, $[\alpha]_D^{20}$ +32.1° (*c* 0.6, Chloroform).

Anal. Ber. für $C_{15}H_{19}NO_9$ (357.3): C, 50.42; H, 5.36; N, 3.92. Gef.: C, 50.48; H, 5.27; N, 3.83.

3,4,5,7-Tetra-O-*acetyl-2,6-anhydro*-D-glycero-D-manno-*heptononitril* (**13**). — 1,2,3,4,6-Penta-*O*-acetyl-α-D-altropyranose[29] (1 g, 2.56 mmol) wird gemäß AAV (*B*) umgesetzt und ergibt Cyanid **13** (0.55 g, 62%), Schmp. 46–47°, $[\alpha]_D^{20}$ +43.1° (*c* 5.8, Chloroform).

Anal. Ber. für $C_{15}H_{19}NO_9$ (357.3): C, 50.42; H, 5.36; N, 3.92. Gef.: C, 50.35; H, 5.40; N, 3.85.

3,4,5,7-Tetra-O-*acetyl-2,6-anhydro*-D-glycero-L-gulo-*heptononitril* (**14**). — 1,2,3,4,6-Penta-*O*-acetyl-α-D-idopyranose[30] (1 g, 2.56 mmol) wird gemäß AAV (*B*) umgesetzt und ergibt Cyanid **14** (73%), Schmp. 119–120°, $[\alpha]_D^{20}$ +34.6° (*c* 2.5, Chloroform).

Anal. Ber. für $C_{15}H_{19}NO_9$ (357.3): C, 50.42; H, 5.36; N, 3.92. Gef.: C, 50.44; H, 5.39; N, 3.87.

3,4,5-Tri-O-*acetyl-2,6-anhydro*-D-*gulononitril* (**18**). — 3,4,5-Tri-*O*-acetyl-2,6-anhydro-1-desoxy-1-nitro-D-gulitol[13] (0.32 g, 1 mmol) wird gemäß AAV (*A*) umgesetzt und führt zu Cyanid **18** (0.22 g, 72%), Schmp. 132–133°, $[\alpha]_D^{20}$ −57.9° (*c* 0.8, Chloroform); Lit.[3] Schmp. 133°, $[\alpha]_D^{20}$ −57.9° (*c* 2.4, Chloroform).

Anal. Ber. für $C_{12}H_{15}NO_7$ (285.3): C, 50.52; H, 5.30; N, 4.91. Gef.: C, 50.49; H, 5.31; N, 4.83.

3,4,5-Tri-O-*acetyl-2,6-anhydro*-D-*galactononitril* (**19**). — 3,4,5-Tri-*O*-acetyl-2,6-anhydro-1-desoxy-1-nitro-D-galactitol[13] (0.32 g, 1 mmol) wird gemäß AAV (*A*) umgesetzt und führt zu sirupösem Cyanid **19** (0.214 g, 75%), $[\alpha]_D^{20}$ −125.2° (*c* 0.8, Chloroform).

Anal. Ber. für $C_{12}H_{15}NO_7$ (285.3): C, 50.52; H, 5.30; N, 4.91. Gef.: C, 50.57; H, 5.33; N, 4.84.

3,4,5-Tri-O-acetyl-2,6-anhydro-L-mannononitril (**20**). — 3,4,5-Tri-*O*-acetyl-2,6-anhydro-1-desoxy-1-nitro-L-mannitol[9,13] (0.32 g, 1 mmol) wird gemäß AAV (*A*) umgesetzt und führt zu Cyanid **20** (0.197 g, 69%), Schmp. 131°, $[\alpha]_D^{20}$ +6.5° (*c* 0.8, Chloroform); Lit.[6] (D-Enantiomer) Schmp. 137°, $[\alpha]_D^{20}$ −5° (Chloroform).

Anal. Ber. für $C_{12}H_{15}NO_7$ (285.3): C, 50.52; H, 5.30; N, 4.91. Gef.: C, 50.48; H, 5.27; N, 4.93.

3,4,5-Tri-O-acetyl-2,6-anhydro-D-allononitril (**21**). — 3,4,5-Tri-*O*-acetyl-2,6-anhydro-1-desoxy-1-nitro-D-allitol[13] (0.32 g, 1 mmol) wird gemäß AAV (*A*) umgesetzt und führt zu sirupösem Cyanid **18** (0.205 g, 72%), $[\alpha]_D^{20}$ −26.8° (*c* 0.5, Chloroform); Lit.[6] $[\alpha]_D^{20}$ −18.0° (*c* 1, Chloroform).

Anal. Ber. für $C_{12}H_{15}NO_7$ (285.3): C, 50.52; H, 5.30; N, 4.91. Gef.: C, 50.55; H, 5.25; N, 4.79.

3,4,5-Tri-O-acetyl-2,6-anhydro-D-altrononitril (**22**). — 3,4,5-Tri-*O*-acetyl-2,6-anhydro-1-desoxy-1-nitro-D-altritol[13] (0.32 g, 1 mmol) werden gemäß AAV (A) umgesetzt und führen zu Cyanid **22** (0.211 g, 74%), Schmp. 72–73°, $[\alpha]_D^{20}$ +93.8° (*c* 0.5, Chloroform).

Anal. Ber. für $C_{12}H_{15}NO_7$ (285.3): C, 50.52; H, 5.30; N, 4.91. Gef.: C, 50.53; H, 5.33; N, 4.87.

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A FULLY SYNTHETIC ROUTE TO THE PAPULACANDINS. STEREOSPECIFIC SPIROACETALIZATION OF A C-1-ARYLATED METHYL GLYCOSIDE*

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ABSTRACT

Lewis acid-catalyzed, hetero Diels-Alder reaction of (*E*)-1-methoxy-3-trimethylsilyloxy-1,3-butadiene with 6-benzoyloxymethyl-2,4-dibenzyloxy benzaldehyde afforded 2-(6-benzoyloxymethyl-2,4-dibenzyloxyphenyl)-2,3-dihydro-4*H*-pyran-4-one. This was converted into a derivative of papulacandin D by a stereospecific, spiroacetalization of a C-1 methoxylated aryl glycoside, [3,5-dibenzoyloxy-(methyl 3-*O*-acetyl-4,6-di-*O*-benzoyl-DL-glucopyranosid-1-yl)phenyl]methyl benzoate.

INTRODUCTION

Papulacandins A–D are antibiotics which were isolated from a strain of *Papularia sphaerosperma*[1]. The papulacandins inhibit the biosynthesis of a D-glucan in yeast spheroplasts. The mechanism of action of papulacandins B in the fungus *Geotrichum lactus* has been traced to its inhibition of the enzyme (1→3)-β-D-glucansynthase[2]. The four antibiotics share several structural themes. A common feature is the spiroacetal type of engagement of a D-glucose residue with 5-hydroxymethyl resorcinol. The *C*-β-glycosyl bond joining the D-glucosyl residue to OH-4 of the resorcinol residue is a most provocative challenge from the synthetic standpoint†.

Another common feature is the presence of a long-chain fatty acyl group at OH-3 of the D-glucose residue. The presence of this type of group is apparently crucial to biological activity[2]. In the A, B, and C isomers, the OH-4 of the D-glucose residue is also linked to a β-D-galactopyranosyl group, OH-6 of which is acylated with a "short" [$C_9C(O)$] trienoyl residue. The D-galactosyl and "short" acyl groups are apparently not crucial for enzymic inhibition, but might well play a role in promoting transport to the active system[2]. The configurations of the stereogenic centers within the long acyl chain are not known in either the absolute or the

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†For an example of a synthesis of an arylated glycoside, see ref. 3.

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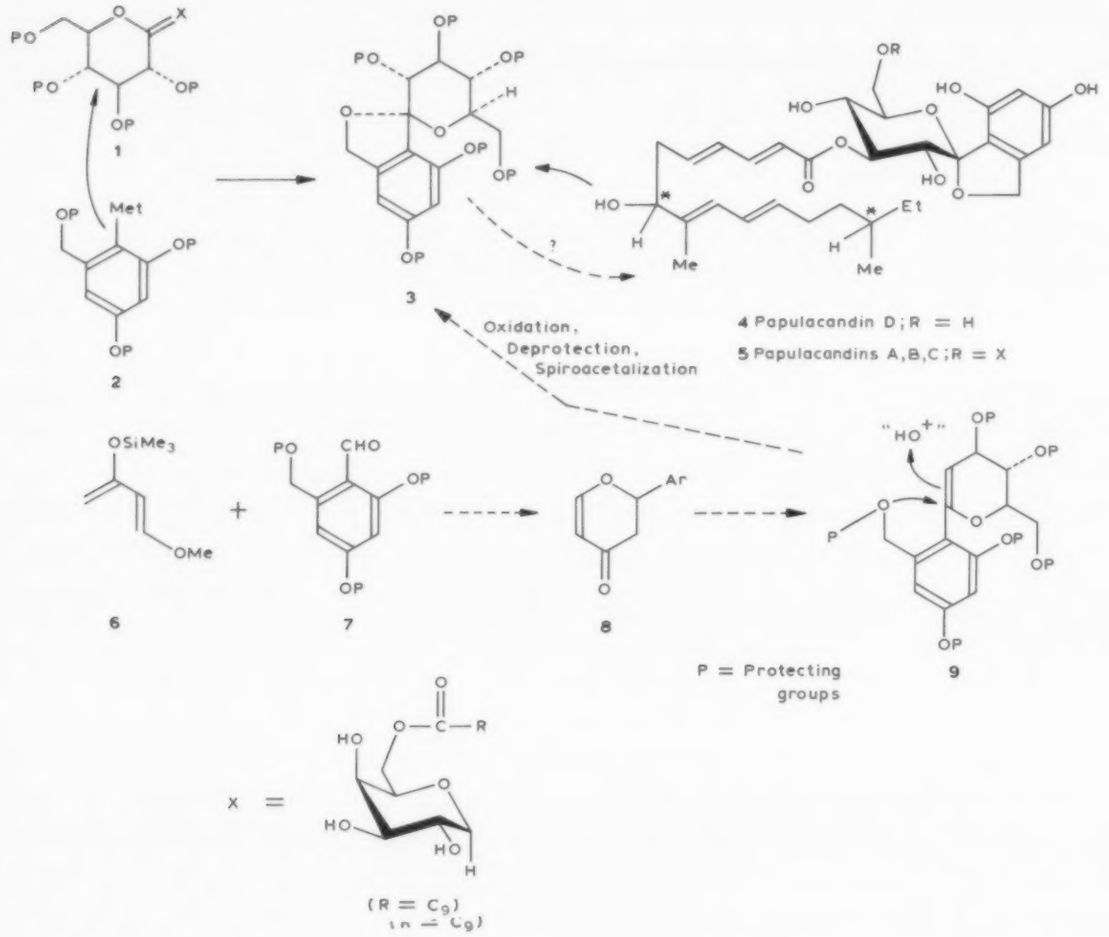
relative sense. These uncertainties further complicate the goal of a total synthesis of any of the "intact" antibiotics.

We have engaged in various studies directed towards the synthesis of complex monosaccharides[4,5]. Many of these compounds possess antibiotic activity and perform important bioregulatory missions. As part of this program, we have initiated some synthetic investigations in the papulacandin area. In this report, we describe a fully synthetic route to the desheptadecanoyl monosaccharide version of papulacandin D, characterized as its hexaacetyl derivative **28**.

An obvious route to the papulacandins would involve coupling of a suitably protected derivative of D-glucose, such as **1**, with a suitably protected organometallic compound **2**. The challenges in such an approach would lie in developing good accesses to the subunits, and in achieving the coupling of the extensively functionalized and possibly hindered components. Of course, the precise nature of X and even the oxidation level of the formal structure **1** are deliberately left unspecified. Some early explorations of such an approach were not encouraging*.



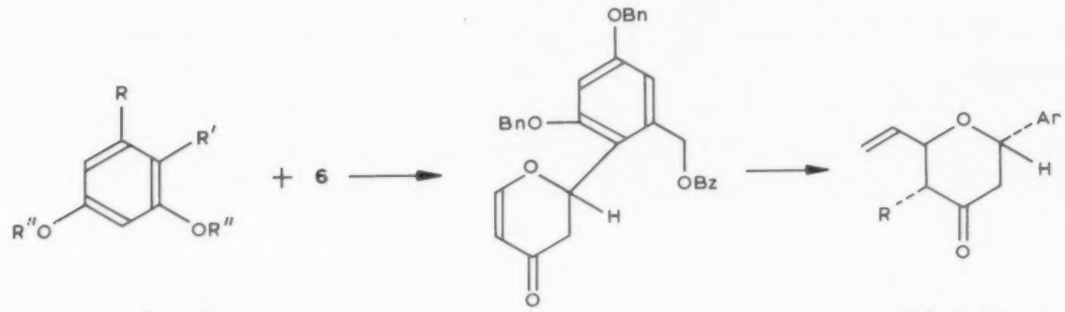
*The aromatic moiety has been metallated and treated with carbon dioxide[6]. Attempts at reacting the aryllithium moiety with pertrimethylalylated glucunolactone gave starting material. Some other potential approaches which were not followed are implied in the work of Eade and Pham[7].

The approach which we decided to follow was radically different in that it contemplated fashioning, by total synthesis, a dihydropyrone of the type **8**. System **8** would be transformed to an intermediate such as **9**. Oxidation of the double bond (in the desired stereochemical sense at C-2), followed by unveiling of the benzyl alcohol in the aromatic segment, would set the stage for spiroacetalization to produce **9***. The plan relied on the supposition that the stereochemical result of the spiroacetalization would be governed, at least at the thermodynamic level, by the anomeric effect[3]. In this way, the configuration at C-1 would conform to that required. Another central element of the projected route was the expectation that the dihydropyrone **8** would be accessible *via* a Lewis acid-catalyzed, hetero Diels–Alder reaction of a suitable benzaldehyde derivative **7** with the parent *trans*-1-methoxy-3-trimethylsilyloxydiene (**6**). The first phase of our inquiry concerned itself with the preparation of the required benzaldehyde and with the hetero Diels–Alder reaction[9].

RESULTS AND DISCUSSION

Commercially available 3,5-dihydroxybenzoic acid was converted into the methyl ester **10**. Bisbenzylation afforded **11**, which upon reduction with lithium aluminum hydride gave rise **12** in 94% yield. Conversion of this compound into its benzoate derivative **13** set the stage for introduction of the crucial aldehyde function by means of a Villsmeier transformation. The key building block **14** was obtained in 66% yield.

Cyclocondensation of **14** with diene **6** occurred under catalysis[10] by $Yb(fod)_3$. The reaction, which took place at 55° in (^{2}H)chloroform over ~3 days, required only ~2 mol of catalyst /100 of the limiting reactant **14**. The yield of apparently homogeneous pyrone **15**, obtained initially as yellow syrup, was 92%.



10 R = CO_2Me, R' = R" = H
11 R = CO_2Me, R' = H, R" = Bn
12 R = CH_2OH, R' = H, R" = Bn
13 R = CH_2OBz, R' = H, R" = Bn
14 R = CH_2OBz, R' = CHO, R" = Bn

15

16 R = H
17 R = OBz

The product of the treatment of vinylmagnesium bromide in oxolane–dimethyl sulfide with cuprous iodide reacted with pyrone **15** to afford, after workup, a 70% yield of the tetrahydropyrone **16**. The vinyl group was to serve as the

*For a recent synthesis of phyllanthocin based on a similar stereospecific spiroacetalization, see ref. 8.

precursor of the hydroxymethyl function (*i.e.*, C-6 of the C-1 arylated D-glycosyl residue). Clearly, it would be advantageous if the kinetically produced enolate resulting from the vinylation could be exploited for introduction of the C-4 oxygen function. While we have not studied the matter exhaustively, several attempts to achieve this result by use of benzoyl peroxide as the direct trapping agent produced only modest and irreproducible yields of the corresponding benzoyloxyketone **17***. Since we now know that the later steps of the synthesis can, in fact, be executed quite efficiently, and since the introduction of this function from the pyranone, in the absence of this kinetic predisposition, was far from satisfactory (*vide infra*), the advantages of oxidative trapping of the kinetically produced enolate from the vinylation of **15** are, in retrospect, apparent.

At this juncture, degradation of the vinyl group to the required C-1 fragment was undertaken. Oxidation of **16** with osmium tetraoxide–sodium metaperiodate produced a very unstable ketoaldehyde, which was immediately treated with lithium tris(3-ethyl-3-pentyloxyaluminum)hydride[13]. The expected selective reduction of the aldehyde function was accomplished. Benzoylation of the primary alcohol afforded a 59% overall yield of **19**.

The next objective became the installation of the oxygen function at C-4. Reaction of ketone **20** with hexamethyldisilazine in the presence of iodotrimethylsilane[14] afforded a two-component mixture of what was assumed to be the isomeric silylenol ethers **21**. This surmise could not be verified, since the gross n.m.r. spectral features of the two components of this unresolved mixture are quite similar. Rather, the crude material was subjected to the action of 4-chloroperoxybenzoic acid[15]. Subsequent treatment with methanol, and then with benzoyl chloride in pyridine, afforded the desired benzoyloxyketone **22**, though only in poor yield. Also isolated from the complex reaction mixture was a comparable quantity of an isomeric product of uncertain structure**.

Treatment of presumed **22** with lithium hexamethyldisilazide, followed by quenching of the reaction with chlorotrimethylsilane, gave a silylenol ether which, in crude form, was subjeced to the action of palladium(II) acetate in acetonitrile[16] to give, in 78% yield, enone **23**. Reduction, followed by acetylation, afforded the pseudoequatorial acetate **25**. Oxidation with 3-chloroperoxybenzoic acid in methanol gave the methoxyhydrin **26** having the *gluco,* rather than *manno,* configuration at C-2 (ref. 17).

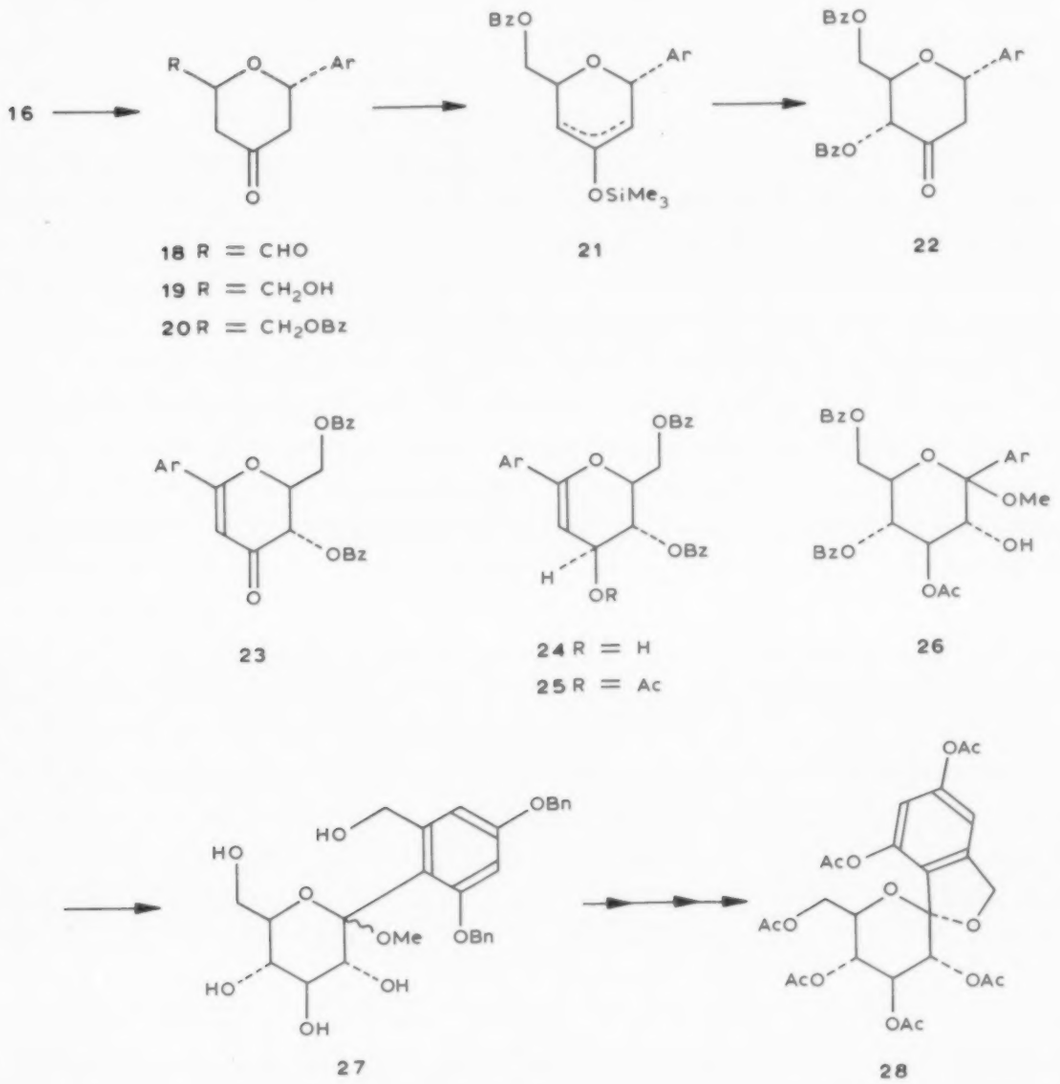
The final phase of the synthesis began with cleavage of all the acyl groups (with methanolic sodium hydroxide). Treatment of the presumed compound **27** with methanolic hydrogen chloride achieved spiroacetalization. The resultant product was acetylated and subjected to debenzylation by hydrogenolysis in the presence of palladium(II) hydroxide[18]. Further acetylation afforded the racemic hexaacetate **28**. The same compound, in optically active form, was obtained as described from papulacandin D (**4**) hydrolysis and acetylation. The chromato-

*For a review on cuprate trapping reactions, see ref. 11; *cf. i.a.*, ref. 12.

**It is not clear at this time whether the compound obtained was a regioisomer or a stereoisomer.

graphic mobility, i.r. and high-field n.m.r. spectra of the synthetic and naturally derived specimens were identical.

In summary, the basis for a synthetic attack on the papulacandins has been established. The spiroacetalization of the C-1 arylated methyl glycoside using a properly placed benzyl alcohol group has been shown to be viable and stereoselective in the required sense. To achieve a practically useful synthesis would require the attainment of major improvements in going from **14** to **23**, or the development of a new route to the late intermediates (*cf.*, **23–26**).



EXPERIMENTAL

General methods. — Melting points were determined with a Thomas–Hoover melting point apparatus and are uncorrected. I.r. spectra were recorded with a Perkin–Elmer spectrophotometer 710 Band 1420. ^{1}H-N.m.r. spectra were recorded with a Varian EM-390 (90 MHz) or Bruker WM-250 (250 MHz) spectrometer.

Mass spectra were obtained with a Hewlett–Packard 5985 spectrometer. High-resolution, exact masses and chemical-ionization mass spectra were obtained with a Kratos MS 80 RFA spectrometer. Reagents and solvents were purified and dried by standard methods and all reactions were run under a nitrogen atmosphere. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

6-Benzoyloxymethyl-2,4-dibenzyloxybenzaldehyde (**14**). — 3,5-Dihydroxybenzoic acid (11.7 g, 75.9 mmol) was dissolved in methanol (100 mL) and concentrated H_2SO_4 (0.2 mL) added. After refluxing for 17 h, the methanol was evaporated and the residue (**10**) was dissolved in acetone (100 mL). Benzyl bromide (29 g, 0.17 mmol) and K_2CO_3 (23 g, 0.17 mmol) were added. After heating under reflux for 6 h, additional portions of benzyl bromide (2.9 g, 17 mmol) and K_2CO_3 (2.0 g, 14 mmol) were added. After stirring for another 10 h, the solid material was filtered off and washed with ether. The solvent was removed *in vacuo* to give methyl 5,5-dibenzyloxybenzoate (**11**; 25.9 g), m.p. 65–66°; $\nu_{max}^{CHCl_3}$ 3020, 1720, 1600, 1300, and 1160 cm^{-1}; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ (7.5–7.0 (m, 12 H), 6.70 (t, 1 H, *J* 3 Hz), 4.96 (s, 4 H), and 3.66 (s, 3 H); m.s.: *m/z* (%) 347 (M^+, 33), 181 (26), and 91 (100). This material was used in the next experiment.

A slurry of lithium aluminum hydride (3.0 g, 79 mmol) in ether (200 mL) was prepared under N_2 and cooled to 0°. Crude **11** (25.9 g, 74 mmol) was added in portions and, after the addition was completed, stirring was continued for 2 h. Water (3 mL), 15% aqueous NaOH (3 mL), and water (9 ML) were added and the solid material was filtered off. Removal of the solvent *in vacuo* gave 3,5-dibenzoyloxybenzyl alcohol (**12**; 22.4 g, 95%) as a white solid, m.p. 73–77°; $\nu_{max}^{CHCl_3}$ 3610, 2920, 1600, and 1160 cm^{-1}; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 7.3 (m, 10 H), 6.5 (m, 3 H, 4.91 (s, 4 H), 4.45 (br. s, 2 H), and 2.4 (br., 1 H); m.s.: *m/z* (%) 320 (M^+, 72), 181 (36), and 91 (100). Compound **12** was used in the next experiment without further purification. Crude **12** (22.4 g, 70 mmol) was dissolved in dichloromethane (100 mL) and the solution cooled to 0°. Triethylamine (11 g, 0.11 mmol) and benzoyl chloride (11 g, 77 mmol) were added and the mixture was stirred for 1 h, at which time it was washed with M HCl, saturated $NaHCO_3$, and NaCl solution, dried ($MgSO_4$), and the solvent removed to give (3,5-dibenzoyloxyphenyl)methyl benzoate (**13**; 29.5 g, 100%) as a white solid, m.p. 67–73°; $\nu_{max}^{CHCl_3}$ 3010, 1715, 1595, 1270, and 1155 cm^{-1}; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 8.08 (dd, 2 H, *J* 8.2 Hz), 7.6–7.2 (m, 13 H), 6.69 (d, 2 H, *J* 2 Hz), 6.60 (+, 1 H, *J* 2 Hz), 5.28 (s, 2 H), and 5.03 (s, 4 H); m.s.: *m/z* (%) 24 (M^+, 6), 181 (11), 105 (16), and 91 (100). This material was used in the next experiment without further purification.

To a flame-dried flask under N_2 was added *N,N*-dimethylformamide (30 mL) and freshly distilled $POCl_3$ (21 g, 0.14 mol) at 0°. After being warmed to room temperature, the mixture was transferred to a flask containing **13** (29.5 g, 70 mmol), dissolved in *N,N*-dimethylformamide (50 mL). After being stirred for 2.5 h at 97°, the mixture was poured into ice–water and extracted with ethyl acetate. The organic layer was separated, washed with water and NaCl solution, dried ($MgSO_4$),

and most of the solvent removed *in vacuo*. Ethyl ether was added and the resulting brown solid (20.9 g, 66%) was filtered off and used without further purification, m.p. 96–98°; $\nu_{max}^{CHCl_3}$ 3040, 1725, 1675, 1605, 1580, 1280, and 1160 cm^{-1}; ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 10.61 (s, 1 H), 8.08 (dd, 2 H, *J* 8, 2 Hz), 7.6–7.2 (m, 13 H), 6.74 (d, 1 H, *J* 2 Hz), 6.58 (d, 1 H, *J* 2 Hz), 5.79 (s, 2 H), 5.12 (s, 2 H), and 5.06 (s, 2 H); m.s.: *m/z* (%) 452 (M^+, 9), 347 (63), 330 (97), 105 (19), and 91 (100).

Anal. Calc. for $C_{29}H_{24}O_5$: C, 76.97; H, 5.34. Found: C, 77.03; H, 5.51.

Cyclocondensation of aldehyde **14** *with diene* **6**. — *2-(6-Benzoyloxymethyl-2,4-dibenzyloxyphenyl)-6-vinyl-2,3-dihydro-4*H*-pyran-4-one* (**16**). To a slurry of the aldehyde **14** (4.42 g, 9.98 mmol) in $CDCl_3$ (15 mL) under N_2, were added the diene **6** (2.0 g, 12 mmol) and $Yb(fod)_3$ (204 mg, 0.19 mmol), and the mixture was heated at 55°. After 14 h, more diene **6** (0.44 g, 2.6 mmol) was added and, after 1 day, another portion (0.53 g, 3.1 mmol). After being heated for another 2 days, the mixture was cooled to room temperature and trifluoroacetic acid (0.5 mL) was added. After stirring for 10 min, the volatiles were removed and the residue chromatographed on silica gel (80 g) with 3:1 hexane–ethyl acetate, to give 2-(6-benzoyloxymethyl-2,4-dibenzyloxyphenyl)-2,3-dihydro-4*H*-pyran-4-one (**15**; 4.69 g, 92%) as a yellow syrup, $\nu_{max}^{CHCl_3}$ 3010, 1715, 1670, 1595, and 1270 cm^{-1}; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 8.03 (dd, 2 H, *J* 2, 8 Hz), 7.7–7.3 (m, 14 H), 6.80 (d, 1 H, *J* 2.4 Hz), 6.67 (d, 1 H, *J* 2.4 Hz), 6.03 (dd, 1 H, *J* 15.4, 3.7 Hz), 5.57 (d, 1 H, *J* 12.9 Hz), 5.48 (dd, 1 H, *J* 6.1, 1 Hz), 5.42 (d, 1 H, *J* 12.9 Hz), 5.11 (d, 1 H, *J* 11.9 Hz), 5.07 (s, 2 H), 5.06 (d, 1 H, *J* 11.7 Hz), 3.48 (dd, 1 H, *J* 17.2, 15.4 Hz), and 2.52 (ddd, 1 H, *J* 1, 3.7, 17.2 Hz); m.s.: *m/z* (%), 520 (M^+, 9), 398 (44), 307 (63), 237 (96), and 91 (100).

To a flame-dried flask under N_2 was added CuI (2.564 g, 13.5 mmol), oxolane (25 mL), and dimethyl sulfide (3.3 g, 51 mmol). The clear colorless solution was cooled to −78°, and vinylmagnesium bromide (27 mL of a M solution in oxolane (27 mmol)) was added. The dihydropyrone **15** (3.47 g, 6.7 mmol) was added in oxolane (20 mL), and the mixture stirred for 1.5 h. Ether and saturated NH_4Cl were added, the organic layer was separated, washed with 9:1 NH_4Cl–NH_4OH and NaCl solution, dried ($MgSO_4$), and the solvent removed. Chromatography on silica gel (90 g) with 2:1 hexane–ethyl acetate gave **16** (2.57 g, 70%) as a white solid, m.p. 115–117°; $\nu_{max}^{CHCl_3}$ 3005, 1715, 1605, 1270, and 1150 cm^{-1}; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 8.04 (dd, 2 H, *J* 2, 8 Hz), 7.6–7.2 (m, 13 H), 6.76 (d, 1 H, *J* 2.4 Hz), 6.59 (d, 1 H, *J* 2.4 Hz), 5.90 (ddd, 1 H, *J* 4.4, 10.9, 17.5 Hz), 5.73 (d, 1 H, *J* 12.9 Hz), 5.64 (dd, 1 H, *J* 3.9, 10.4 Hz), 5.43 (d, 1 H, *J* 12.9 Hz), 5.3–5.1 (m, 2 H), 5.05 (d, 1 H, *J* 12.1 Hz), 5.00 (s, 2 H), 4.99 (d, 1 H, *J* 12.1 Hz), 4.85 (m, 1 H), 3.13 (dd, 1 H, *J* 10.4, 15.2 Hz), 2.70 (dd, 1 H, *J* 6.3, 15.1 Hz), and 2.4–2.7 (m, 2 H); m.s.: *m/z* (%) 548 (M^+, 4), 426 (36), 357 (46), 335 (90), and 91 (100).

Anal. Calc. for $C_{35}H_{32}O_6$: C, 76.62; H, 5.87. Found: C, 76.94; H, 5.80.

trans-*5-Benzoyloxy-6-benzoyloxymethyl-2-(6-benzoyloxymethyl-2,4-dibenzyloxyphenyl)-2,3,5,6-tetrahydro-4*H*-pyran-4-one* (**22**). — The vinylpyranone **16** (1.04 g, 1.9 mmol) was dissolved in 1,4-dioxane (22 mL) and water (7 mL). Osmium

tetraoxide (0.5 mL of a 10 mg/mL solution in oxolane, 0.02 mmol) and $NaIO_4$ (1.34 g, 6.2 mmol) were added, and the mixture was stirred for 20 h. Water was added, and the mixture was stirred for 20 h. Water was added, and the mixture extracted with ether, the organic layer washed with water and NaCl solution, dried ($MgSO_4$), and most of the solvent removed *in vacuo*.

The crude aldehyde **18** was dissolved in oxolane (25 mL) under N_2 and cooled to −78°. Lithium tris(3-ethyl-3-pentyloxy)aluminum hydride (11 mL of a 0.57M solution in oxolane, 6.3 mmol) was added. After stirring for 2 h, the reaction was quenched with ethyl acetate and M HCl. The organic layer was washed with NaCl solution, dried (Na_2SO_4), and the solvent removed *in vacuo*. Chromatography on silica gel (20 g) with 2:1 hexane–ethyl acetate gave 6-benzoyloxymethyl-2-(6-benzoyloxymethyl-2,4-dibenzyloxyphenyl)-2,3,5,6-tetrahydro-4*H*-pyran-4-one (**20**) as a white foam (730 mg, 59%); $\nu_{max}^{CHCl_3}$ 3020, 3000, 1740, 1720, 1600, and 1270 cm^{-1}; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 8.03 (dd, 2 H, *J* 2, 8 Hz), 7.98 (dd, 2 H, *J* 2, 8 Hz), 7.7–7.3 (m, 16 H), 6.77 (d, 1 H, *J* 2.4 Hz), 6.59 (d, 1 H, *J* 2.4 Hz), 5.85 (dd, 1 H, *J* 5.2, 7.9 Hz), 5.62 (d, 1 H, *J* 12.9 Hz), 5.48 (d, 1 H, *J* 12.9 Hz), 5.03 (s, 2 H), 5.02 (s, 2 H), 4.6–4.3 (m, 3 H), 3.17 (dd, 1 H, *J* 7.9, 16.0 Hz), 2.70 (dd, 1 H, *J* 5.2, 16.0 Hz), 2.6 (m, 1 H), and 2.53 (dd, 1 H, *J* 6, 16 Hz).

The pyranone **20** (508 mg, 0.77 mmol) was dissolved in benzene (5 mL) under N_2. Hexamethyldisilazane (0.18 g, 1.1 mmol) and iodotrimethylsilane (6.17 g, 0.8 mmol) were added. The slurry was stirred for 40 min and the solvent removed *in vacuo*. The mixture was filtered through a plug of silica gel with 2:1 hexane–ethyl acetate and the solvent removed *in vacuo* to give two compounds (see **21**) as a 2:1 mixture. The crude material was dissolved in benzene (5 mL), 3-chloroperbenzoic acid (171 mg, 1 mmol) added, and the mixture stirred for 30 min. The solvent was removed *in vacuo*, the gummy residue dissolved in methanol (2 mL) and oxolane (1 mL), and the solution stirred for 6 h. The solvent was removed *in vacuo*, the gum was dissolved in ethyl acetate, the solution washed with aqueous $NaHCO_3$ and NaCl, dried (Na_2SO_4), and the solvent removed *in vacuo*. Chromatography on silica gel (20 g) with 2:1 hexane–ethyl acetate gave a 1:1 mixture (240 mg) of two products which were dissolved in pyridine (1 mL) and benzoyl chloride (72 mg, 0.5 mmol). After being stirred for 2 h, the slurry was dissolved in ethyl acetate and washed with M HCl, saturated $NaHCO_3$, and NaCl solution. Medium pressure liquid chromatography on silica gel with 5:2 hexane–ethyl acetate gave **22** (99 mg, 17%), m.p. 154–155°; $\nu_{max}^{CHCl_3}$ 3010, 1730, 1715, 1600, and 1265 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 8.05 (dd, 2 H, *J* 2, 8 Hz), 7.95 (dd, 2 H, *J* 2, 8 Hz), 7.90 (dd, 2 H, *J* 2, 8 Hz), 7.7–7.3 (m, 19 H), 6.78 (d, 1 H, *J* 2.4 Hz), 6.51 (d, 1 H, *J* 2.4 Hz), 5.91 (t, 1 H, *J* 5.4 Hz), 5.78 (d, 1 H, *J* 9.4 Hz), 5.55 (d, 1 H, *J* 12.9 Hz), 5.46 (d, 1 H, 12.9 Hz), 5.16 (d, 1 H, *J* 14.1 Hz), 5.02 (d, 1 H, *J* 14.1 Hz), 4.96 (s, 2 H), 4.6–4.4 (m, 3 H), and 3.16 (d, 2 H, *J* 5.4 Hz).

Anal. Calc. for $C_{48}H_{40}O_{10}$: C, 74.26; H, 5.19. Found: C, 74.10; H, 5.29.

A comparable amount of an unidentified material was also obtained.

[*3,5-Dibenzoyloxy-2-(methyl 3-*O*-acetyl-4,6-di-*O*-benzoyl-*DL*-glucopyranosid-*

1-yl)phenyl methyl benzoate (**26**). — To a flame-dried flask under N_2 was added oxolane (2 mL), hexamethyldisilazane (69 mg, 0.49 mmol), and butyllithium (0.25 mL of a 1.6M solution in hexane, 0.4 mmol). After being stirred for 20 min, the solution was cooled to −78°, and a solution of **22** (105 mg, 0.14 mmol) in oxolane (1 mL) and hexamethylphosphoramide (75 mg, 0.42 mmol) was added. To this, freshly distilled chlorotrimethylsilane (86 mg, 0.79 mmol) was added and the reaction was quenched 15 min later with ether and saturated $NaHCO_3$. The organic layer was separated, washed with water and NaCl solution, dried (Na_2SO_4), and the solvent removed *in vacuo*. To the crude silylenol ether, dissolved in freshly distilled acetonitrile (2 mL), was added palladium (II) acetate (47 mg, 0.21 mmol), and the mixture stirred for 24 h. The solvent was removed *in vacuo* and the residue chromatographed on silica gel (8 g) with 3:1 hexane–ethyl acetae to give 3-benzoyloxy-2-benzoyloxymethyl-6-(6-benzoyloxymethyl-2,4-dibenzyloxyphenyl)-2,3-dihydro-4*H*-pyran-one (**23**; 82 mg, 78%) which contained ~10% of **22**; $\nu_{max}^{CHCl_3}$ 3010, 1720, 1680, 1600, and 1265 cm^{-1}; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 8.2–8.0 (m, 6 H), 7.7–7.3 (m, 19 H), 6.77 (d, 1 H, *J* 2.0 Hz), 6.61 (d, 1 H, *J* 2.0 Hz), 6.01 (d, 1 H, *J* 12.8 Hz), 5.83 (s, 1 H), 5.47 (d, 1 H, *J* 12.8 Hz), 5.38 (d, 1 H, *J* 12.8 Hz), 5.08 (s, 2 H), 5.06 (s, 2 H), 5.0 (m, 1 H), 4.72 (dd, 1 H, *J* 2.4, 12.7 Hz), 4.54 (dd, 1 H, *J* 48, 12.7 Hz); m.s.c.i.: *m/z* (%) 775 (M^+ + 1, 12), 244 (14), 140 (60), 105 (100), and 80 (69).

Compound **23** (82 mg, 0.11 mmol) was dissolved in oxolane (3 mL) under N_2 the solution cooled to −78°, diisobutyl aluminum hydride (0.6 mL of a M solution in hexane, 0.6 mmol) added, and the mixture stirred for 1 h. Some starting material remained and more diisobutyl aluminum hydride (0.5 mL of a M solution in hexane, 0.5 mmol) was added. After stirring for 1 h, the reaction was quenched with ethyl acetate and M HCl. The organic layer was separated, washed with NaCl solution, dried (Na_2SO_4), and the solvent removed. The crude residue (**24**) was dissolved in pyridine (0.5 mL) and acetic anhydride (0.05 mL) and the mixture stirred for 10 h. The solvent was removed and the residue chromatographed on silica gel (5 g) with 3:1 hexane–ethyl acetate to give [2-(3-acetyl-1,5-anhydro-4,6-di-*O*-benzoyl-2-deoxy-DL-*arabino*-hex-1-enit-3-yl)-3,5-dibenzoyloxyphenyl]methyl benzoate (**25**) (49 mg, 56%), $\nu_{max}^{CHCl_3}$ 3020, 1740, 1600, and 1270 cm^{-1}; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 8.2–7.9 (m, 6 H), 7.6–7.3 (m, 19 H), 6.75 (d, 1 H, *J* 2.2 Hz), 6.58 (d, 1 H, *J* 2.2 Hz), 5.70 (t, 1 H, *J* 5.5 Hz), 5.62 (t, 1 H, *J* 4 Hz), 5.45 (m, 2 H), 5.17 (d, 1 H, *J* 3.7 Hz), 5.07 (s, 3 H), 5.04 (s, 2 H), 4.74 (m, 1 H), 4.66 (dd, 1 H, *J* 4.1, 12.1 Hz), 4.55 (dd, 1 H, *J* 6.1, 12.1 Hz), and 1.94 (s, 3 H); m.s.c.i. (NH_3): *m/z* 836 (M^+ + 18).

The glycal **25** (40 mg, 0.060 mmol) was dissolved in 10:1 methanol–oxolane (2 mL) and 3-chloroperoxybenzoic acid (13 mg, 0.07 mmol) was added. The mixture was stirred for 2 d, the solvent removed *in vacuo*, and the residue dissolved in ethyl acetate. The solution was washed with 10% $NaHCO_3$ and NaCl solution, dried (Na_2SO_4), and the solvent removed *in vacuo*. Chromatography on silica gel (3 g) with 2:1 hexane–ethyl acetate gave a mixture (43 mg, 82%) of methyl glyco-

sides (**26**) $\nu_{max}^{CHCl_3}$ 3020, 1725, 1605, and 1270 cm^{-1}; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 8.1–7.9 (m, 6 H), 7.7–7.3 (m, 19 H), 6.79 (d, 1 H, *J* 2.3 Hz), 6.63 (d, 1 H, *J* 2.23 Hz), 5.87 (d, 1 H, *J* 13.6 Hz), 5.68 (t, 1 H, *J* 9.3 Hz), 5.5 (t, 1 H, *J* 9.2 Hz), 5.44 (d, 1 H, *J* 13.6 Hz), 5.07 (m, 2 H), 4.98 (s, 2 H), 4.63 (dd, 1 H, *J* 1.0, 11.8 Hz), 4.48 (dd, 1 H, *J* 4.7, 11.8 Hz), 4.3 (m, 1 H), 4.1 (m, 1 H), 3.30 (s, 3 H), and 1.94 (s, 3 H).

Conversion of methyl glycosides **26** *to spiro[5,7-diacetoxyisobenzofuran-1-(3*H*),1'-(2',3',4',6'-tetra-*O*-acetyl-*DL*-glycopyranose)* (**28**). — The mixture **26** (32 mg, 0.037 mmol) was dissolved in 0.4M methanolic NaOH (1 mL) and stirred for 5 h; 1.1M methanolic HCl (1 mL) was added, followed by solid $NaHCO_3$. The material was filtered through Na_2SO_4 with chloroform and the solvent removed *in vacuo*. Chromatography on silica gel (1 g) with 9:1 chloroform–methanol gave a material (22 mg) which was dissolved in ethyl acetate (2 mL). $Pd(OH)_2$ on C (4 mg) was added and the mixture placed under an atmosphere of H_2. After being stirred for 5 h, the mixture was filtered through Celite and the solvent removed *in vacuo*. The residue was dissolved in pyridine (0.5 mL) and acetic anhydride (50 μL), and stirred for 7 h. The solvent was removed *in vacuo* and the residue chromatographed on silica gel (1 g) with 1:1 hexane–ethyl acetate to give 8 mg (38%) hexaacetate **28**; $\nu_{max}^{CHCl_3}$ 1755, 1380, and 1220 cm^{-1}; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 7.01 (d, 1 H, *J* 1.8 Hz), 6.93 (d, 1 H, *J* 1.8 Hz), 5.71 (d, 1 H, *J* 10 Hz), 5.60 (t, 1 H, *J* 10 Hz), 5.25 (t, 1 H, *J* 10 Hz), 5.2 (m, 2 H), 4.3 (m, 2 H), 4.05 (m, 1 H), 2.41 (s, 3 H), 2.3 (s, 3 H), 2.07 (s, 3 H), 2.06 (s, 3 H, 2.02 (s, 3 H), and 1.80 (s, 3 H); n.s.: *m/z* (%) 552 (M^+, 1), 450 (2), 366 (16), 176 (75), 119 (95), and 91 (100).

Anal. Calc. for $C_{25}H_{28}O_{14}$: Mol.wt. 552.1479. Found: 552.1483.

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SYNTHESIS OF *C*-PENTO, -HEXO-, AND -HEPTULO-PYRANOSYL COMPOUNDS *VIA* RADICAL C–C BOND-FORMATION REACTIONS

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ABSTRACT

C-Glycosyl compounds were synthesized by addition of pyranosyl radicals to acrylonitrile, fumarodinitrile, or methacrylonitrile in the presence of tributyltin hydride in 34–75% yields. The pyranosyl radicals were generated by abstraction of a bromine atom or a nitro group by tributyltin radicals. The stereoselectivity of the C–C bond to the pyranosyl radicals was, in most cases, remarkably high, but hexopyranosyl and pentopyranosyl radicals showed different selectivity. Whereas the tetra-*O*-acetylglucosyl radical reacted with acrylonitrile preponderantly to give a *C*-glycosyl compound having the newly formed C–C bond in an axial position, the tri-*O*-acetylxylosyl radical gave a *C*-glycosyl compound having an equatorial C–C bond. In the tetra-*O*-acetylmannosyl radical, the axial acetoxy substituent, adjacent to the radical center, led exclusively to a compound having a *trans* C–C bond, whereas the tri-*O*-acetyllyxosyl radical showed *trans*- and *cis*-addition to acrylonitrile in a 7:3 ratio.

INTRODUCTION

The formation of C–C bonds *via* addition of an alkyl radical **3** to an alkene (**2**) has proved to be a very versatile method for the synthesis of target molecules under mild conditions[1]. For a successful application of this reaction, the adduct radical **1** is converted into compounds before these can then further react with alkenes to give polymers. Several methods have been developed to intercept this unwanted polymerization side-reaction, for example, by trapping with atom donors[1] or by radical-fragmentation reactions[2]. A useful trap is tributyltin hydride that reacts with the adduct radical **1** to give **5** and the tin radical **4**. With a suitably substituted educt **6**, *e.g.*, halides, selenides, or xanthates, the tributyltin radical regenerates the alkyl radical **3**.

We have previously used this tin method for the selective generation and the C–C bond-formation reactions of carbohydrate radicals[3]. We describe herein the

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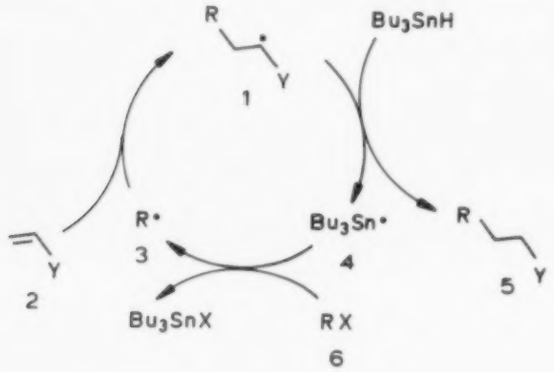
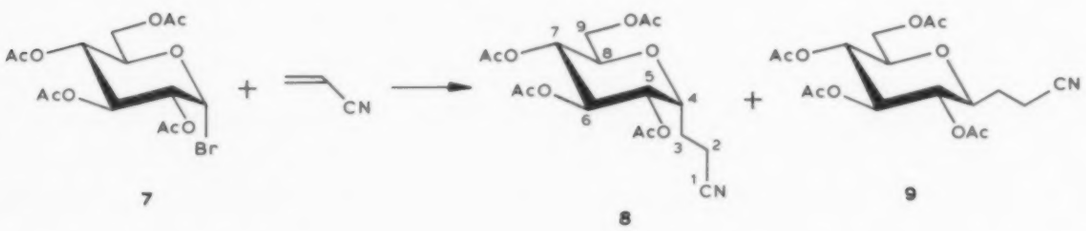
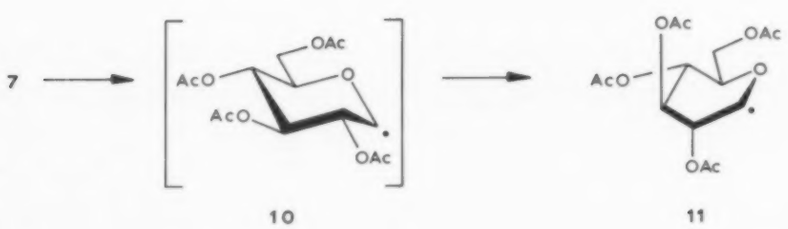
synthesis of *C*-hexopyranosyl, -heptulopyranosyl, and -pentopyranosyl derivatives.



RESULTS AND DISCUSSION

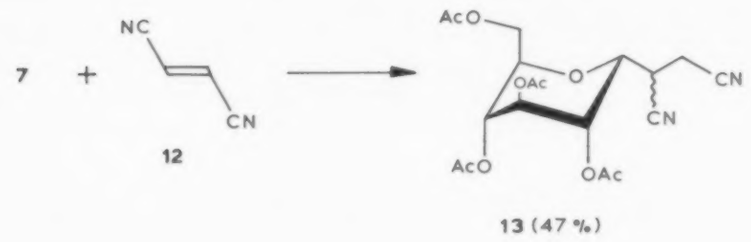
The reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**7**) with tributyltin hydride and acrylonitrile gave the *C*-α-D- (**8**) and -β-D-glucopyranoside **9** in 75% yield and a 93:7 ratio. With photolytical initiation of the radical-chain reaction in ether, most of the product **8** precipitated directly from the solution. The axial orientation of the cyanoethyl group was deduced from the ^{1}H-n.m.r. coupling $J_{4,5}$ 5.2 Hz, whereas the equatorial acetoxy and acetoxymethyl groups led to diaxial-coupling constants $J_{5,6} = J_{6,7} = J_{7,8}$ 8.3 Hz. The minor anomer **9**, which was isolated by column chromatography, only exhibited the diaxial-coupling constants $J_{4,5} = J_{5,6}$ 9.6, $J_{6,7}$ 9.4, and $J_{7,8}$ 9.8 Hz at the pyranosyl ring. As a side-product, tetra-*O*-acetyl-1,5-anhydro-D-glucitol was formed, in 5% yield, by reduction of **7**.

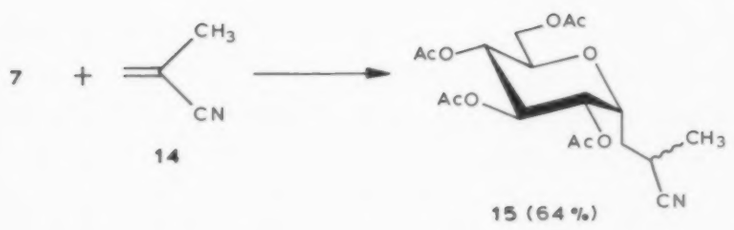


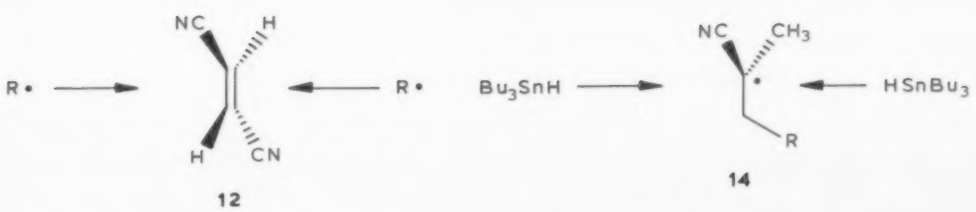


The high selectivity of formation of the axially substituted *C*-glucopyranosyl compound **8** was surprising because equatorially substituted glycopyranosyl radi-

cals having radical centers at C-2, C-3, and C-4 are attacked by alkenes preponderantly from the equatorial side[4]. The reason for the opposite selectivity of the reaction with **7** may be explained by a slightly twisted boat conformation **11** for the intermediate radical instead of the chair conformation **10**. This was shown by the small β-coupling constant in the e.s.r. spectrum[5]. The twist-boat conformation **11** is stabilized by the interaction between the SOMO (single-occupied molecular orbital) of the radical center and the LUMO (lowest-unoccupied molecular orbital) of the adjacent axial C–OAc bond. This interaction is very effective in radical **11** because the neighboring oxygen atom increases the SOMO and, therefore, decreases the SOMO–LUMO energy difference. The preponderant formation of the axially substituted compound **8** resulted from a quasi-equatorial attack at radical **11**. Conversion from the twist-boat to the chair form then led to **8**. The formation of compounds having an axial substituent *via* radical **11** is analogous to cationic reactions. Lemieux *et al.*[6] and Lewis *et al.*[7] explained the rates and stereochemical relations of ionic reactions at the anomeric carbon atom of D-glucose derivatives *via* a cationic intermediate having a conformation that resembles that of radical **11**.

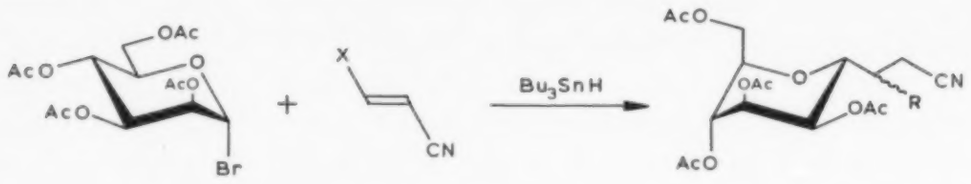




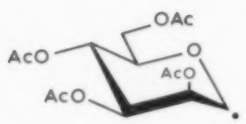


Reactions with 1,2- or 1,1-disubstituted alkenes induce a new chiral center at the side-chain of the oxolane system. Thus, in reactions with fumarodinitrile (**12**) and methacrylonitrile (**14**) in which only axially-substituted products could be isolated, two diastereomers were obtained in 33:17 and 61:39 ratios, respectively. The

small ratio of the compounds obtained shows that the asymmetric induction, caused by the chiral pyranosyl ring, on the diastereoface selectivity in the side chain is low. However, it was not possible to deduce from the n.m.r. data the side-chain chirality of the minor and the major diastereomer. The coupling constants $J_{5,6}$, $J_{6,7}$, and $J_{7,8}$ of **13** (3.4–4.7 Hz) were too far from diaxial couplings. Therefore, we concluded that the $^4C_1$ (D) chair of **7** had been converted into a $^1C_4$ (D)-like conformation in **(13)**.



16 (X = H or CN) **17** R = H (68 %) **18** R = CN (34 %)



19

Similarly to the D-glucosyl system, 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide (**16**) reacted with a high selectivity at the pyranosyl ring and a low selectivity at the side chain. The mannosyl radical was attacked by alkenes with an even higher stereoselectivity than the glucosyl radical and only isomers **17** and **18** were detected. In view of the diaxial coupling constant $J_{4,5}$ 9.4 Hz and the diequatorial or axial–equatorial couplings $J_{5,6}$, $J_{6,7}$, and $J_{7,8'}$ which are between 1.8 and 3.6 Hz, the $^1C_4$ (D) chair conformation was attributed to the fumarodinitrile adduct **18**. For the acrylonitrile aduct **17**, the coupling constants $J_{4,5}$ 6.1 Hz and $J_{5,6}$, $J_{6,7}$, and $J_{7,8}$ 3.4–6.3 Hz suggested a conformation that is between a $^1C_4$ (D) chair and a twist-boat conformation. The selective formation of **17** and **18** may be explained by the intermediate mannosyl radical **19** for which the e.s.r. analysis indicated a $^4C_1$ (D) conformation[5]. In the mannosyl radical **19**, the SOMO of the radical and the LUMO of the adjacent, axial C–OAc bond are already in one plane and may, therefore, lead to a stabilizing interaction without change of the $^4C_1$ (D) conformation. The axial acetoxy group directs the attack of the alkene to the axial side. Ring inversion then gives the isomers **17** and **18** having the $^1C_4$ (D) conformation.

The reaction of the D-*gluco*-heptulopyranose derivative **20** (synthesized according to the procedure of Baumberger and Vasella[8]) with tributyltin hydride and acrylonitrile gave **21** as the only isolable compound. Its structure, determined by X-ray crystallography (Fig. 1), showed that an axial C–C bond is formed. Thus, the

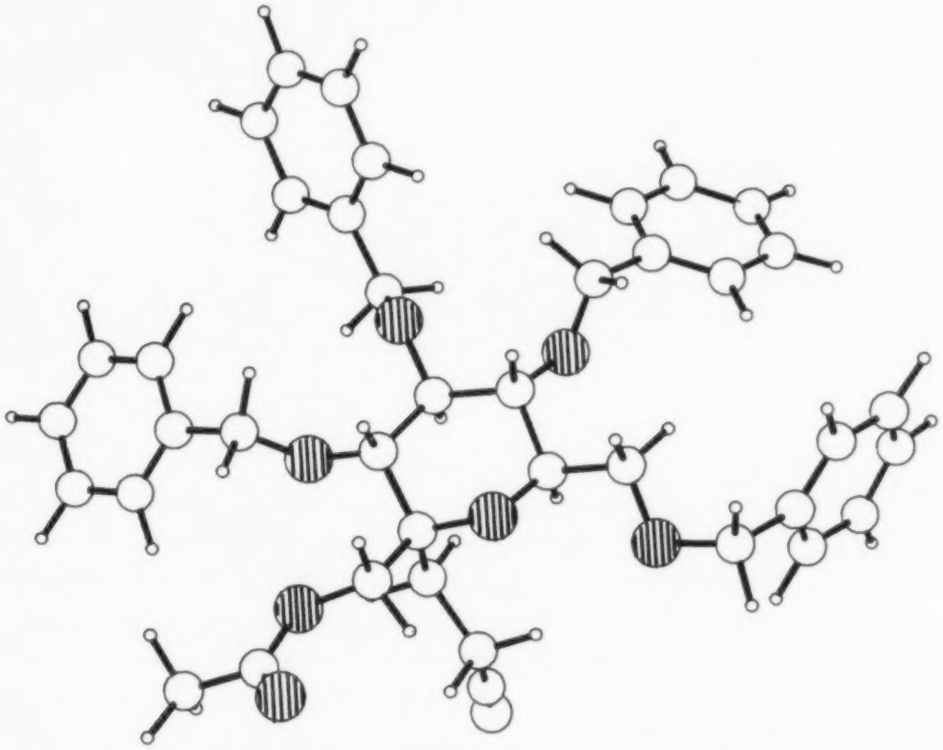
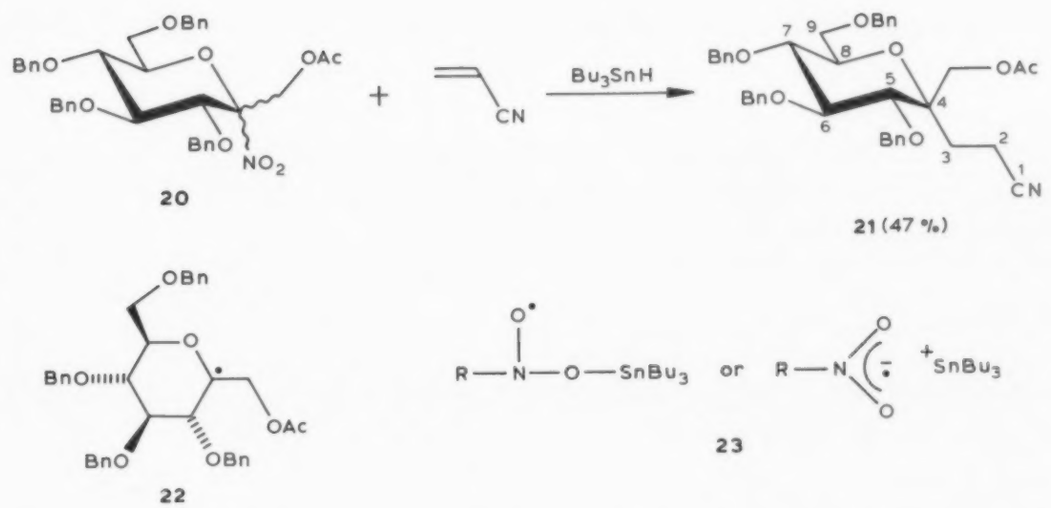
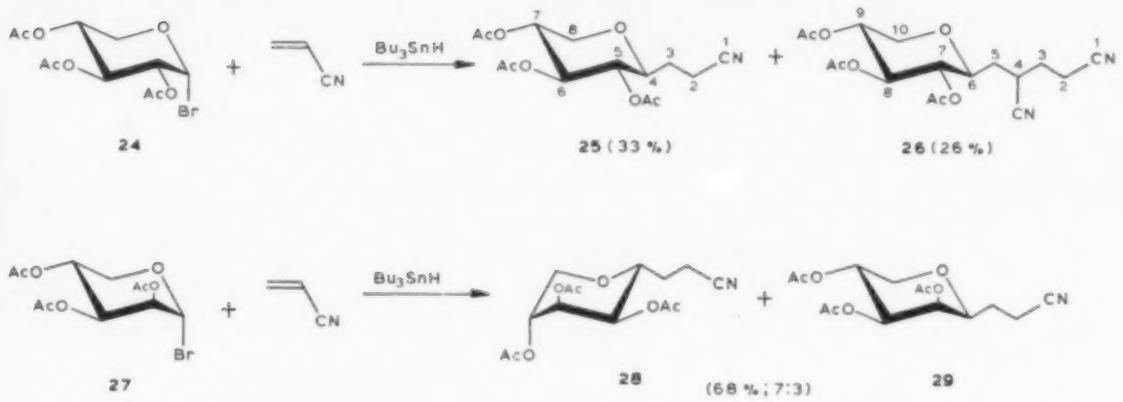


Fig. 1. Crystal structure of **21**. The oxygen atoms are hatched.



stereochemical outcome of the reaction of the D-*gluco*-heptulopyranosyl radical **22** is similar to that of the D-glucopyranosyl radical **11**. The conformation of the tertiary radical **22** could not be determined because the e.s.r. spectrum showed only signals of radical **23**, generated by the attack of the tin radical on the nitro compound[9].

2,3,4-Tri-*O*-acetyl-α-D-xylopyranosyl bromide (**24**) and 2,3,4-tri-*O*-acetyl-α-D-lyxopyranosyl bromide (**27**) gave **25** and **26**, and **28** and **29**, respectively, in the



radical-chain reaction with acrylonitrile. All products have conformations in which the newly formed C–C bonds are in equatorial position. This was shown by the large diaxial coupling-constants $J_{4,5}$ 9.6, 9.5, and 9.9 Hz for **25**, **26**, and **28**, respectively, and the small coupling $J_{4,5}$ 1.1 Hz for **29**. The reason for the relatively large amount of the 2:1 addition product in the reaction with **24** is not known. Although the e.s.r. spectra of the pentopyranosyl radicals are not much different from those of the hexopyranosyl radicals[10], the stereochemical relations differ considerably from each other. The D-xylosyl bromide **24** reacted with a selectivity that is opposite to that of the D-glucosyl bromide **7**, and the D-lyxosyl bromide **27** gave 30% of the *cis* isomer **29**, although the D-mannosyl bromide **16** gave exclusively the *trans* compound **17**.

Thus, the reactions with pentopyranosyl rings led, to a larger extent, to the more stable diastereomers, in which less substituents are axial, than did the reactions with hexopyranosyl rings. Maybe the intermediate pentopyranosyl radicals are so flexible, owing to the absence of an acetoxymethyl substituent at C-5, that the stability of the compounds formed already plays a role in the transition states of the C–C bond-forming reactions.

EXPERIMENTAL

General methods. — Melting points were determined with a Büchi apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. I.r. spectra (KBr discs) were recorded with a Perkin–Elmer 297 spectrometer and ^{1}H-n.m.r. spectra with a Bruker WM-300 spectrometer (300 MHz) for solutions in $CDCl_3$. Analyses were performed with a Perkin–Elmer Sigma 3 gas chromatograph; column chromatography used silica gel (Machery and Nagel, 40–63 μm).

*5,6,7,9-Tetra-*O*-acetyl-4,8-anhydro-2,3-dideoxy-*D-glycero-D-ido-*nonononitrile* (**8**) *and 5,6,7,9-tetra-*O*-acetyl-4,8-anhydro-2,3-dideoxy-*D-glycero-D-gulo-*nonononitrile* (**9**). (*Photolytic initiation*). — To a a solution of compound **7** (ref. 11; 50 mmol, 20.6 g) in anhydrous ether (100 mL) at reflux were added, under N_2, acrylonitrile (250 mmol, 13.5 g) and tributyltin hydride (55 mmol, 16.0 g). After a 4-h

irradiation with a sun lamp or a high-pressure mercury lamp, the precipitate was filtered off, further acrylonitrile (120 mmol, 6.6 g) and tributyltin hydride (20 mmol, 5.8 g) were added, and the filtrate was again irradiated. When the starting bromide **7** had completely reacted, the cold mixture was filtered, and the combined precipitates gave **8** (8.6 g, 45%) after crystallization from ether. The filtrates were evaporated, the residue was dissolved in acetonitrile (50 mL), and the solution extracted three times with pentane (50 mL each). The acetonitrile solution was evaporated and the resulting sirup flash-chromatographed on silica gel (1:1 ethyl acetate–hexane). The first fraction contained tetra-*O*-acetyl-1,5-anhydro-D-glucitol (3.5 g, 21%), the second pure **9** (950 mg, 5%), and the third additional **8** (2.5 g, 13%). The ratio of **8** to **9** of the mixture before work up was 93:7 (g.l.p.c.). In a synthesis with **7** (2.0 g) in boiling oxolane (50 mL), **8** (75%) was isolated in 75% yield (1.4 g) by flash-chromatography.

Compound **8**. Colorless crystals (from ether), m.p. 121–123°, $[\alpha]_D^{20}$ + 66.2° (*c* 0.7, chloroform); ν_{max}^{KBr} 2240 (C≡N) and 1745 (C=O) cm^{-1}; ^{1}H-n.m.r.: δ 1.84–1.95 (m, 1 H, H-3a), 2.05 (s, 6 H, OAc), 2.09 (s, 3 H, OAc), 2.11 (s, 3 H, OAc), 2.05–2.24 (m, 1 H, H-3b), 3.46 (m, 2 H, H_2-2), 3.88 (ddd, 1 H, $J_{7,8}$ 8.3, $J_{8,9a}$ 2.9, $J_{8,9b}$ 5.8 Hz, H-8), 4.12 (dd, 1 H, $J_{8,9b}$ 5.8, $J_{9a,9b}$ 12.2 hz, H-9b), 4.23 (m, 1 H, H-4), 4.32 (dd, 1 H, $J_{8,9a}$ 5.8, $J_{9,9b}$ 12.2 Hz, H-9a), 4.98 (t, 1 H, $J_{6,7} = J_{7,8}$ 8.3, H-7), 5.09 (dd, 1 H, $J_{4,5}$ 5.2, $J_{5,6}$ 8.3 Hz, H-5), and 5.23 (t, 1 H, $J_{5,6} = J_{6,7}$ 8.3, H-6).

Anal. Calc. for $C_{17}H_{23}NO_9$: C, 52.98; H, 6.02; N, 3.63. Found: C, 52.80; H, 6.01; N, 3.63.

Compound **9**. Colorless crystals, m.p. 117–119°, $[\alpha]_D^{25}$ −19.6° (*c* 1.0, chloroform); ν_{max}^{KBr} 2240 (C≡N) and 1745 (C=O) cm^{-1}; ^{1}H-n.m.r.: δ 1.79 (m, 1 H, H-3a), 1.92 (m, 1 H, H-3b), 2.00 (s, 3 H, OAc), 2.03 (s, 3 H, OAc), 2.07 (s, 3 H, OAc), 2.09 (s, 3 H, OAc), 2.52 (m, 2 H, H_2-2), 3.56 (dt, 1 H, $J_{3,4}$ 2.6, $J_{3,4} = J_{4,5}$ 9.6 Hz, H-4), 3.58 (ddd, 1 H, $J_{7,8}$ 9.9, $J_{8,9a}$ 5.0, $J_{8,9a}$ 2.1 Hz, H-8), 4.11 (dd, 1 H, $H_{8,9a}$ 5.0, $H_{9a,9b}$ 12.2 Hz, H-9a), 4.88 (t, 1 H, $J_{4,5} = J_{5,6}$ 9.6 Hz, H-5), 5.05 (t, 1 H, $J_{6,7} = J_{7,8}$ 9.4 Hz, H-7), and 5.20 (dd, 1 H, $J_{5,6}$ 9.6, $J_{6,7}$ 9.4 Hz, H-6).

Anal. Calc. for $C_{17}H_{23}NO_9$: C, 52.98; H, 6.02; N, 3.63. Found: C, 52.85; H, 6.09; N, 3.70.

(*3*RS)-*5,6,7,9-Tetra*-O-*acetyl-4,8-anhydro-3-cyano-2,3-dideoxy*-D-glycero-D-ido-*nonononitrile* (**13**). — To a solution of **7** (7.3 mmol, 3.0 g) and fumarodinitrile **12** (73 mmol, 5.7 g) in toluene (180 mL) were added, at 100° under N_2 within 5 h, a solution of tributyltin hydride (7.9 mmol, 2.3 g) and azoisobutyronitrile (300 mg) in toluene (20 mL). The toluene was destilled off, and the residue dissolved in acetonitrile (300 mL) and extracted three times with pentane (50 mL each). The acetonitrile solution was evaporated, and the residue dissolved in ethyl acetate (20 mL) and chromatographed on silica gel (1:1 ethyl acetate–pentane). The two isomers **13** were isolated in 890 and 490 mg amounts (47%). From the ^{1}H-n.m.r. spectra, it could not be concluded which of these was the [(3*R*)-3-cyano or the (3*S*)-3-cyano]nononononitrile derivative.

Major isomer. Colorless crystals (from ether), m.p. 137–138°, $[\alpha]_D^{20}$ +24.2° (*c*

0.43, chloroform); ν_{max}^{KBr} 2260 (C≡N) and 1740 (C=O) cm^{-1}; ^{1}H-n.m.r.: δ 2.11 (s, 3 H, OAc), 2.12 (s, 6 H, OAc), 2.21 (s, 3 H, OAc), 2.87 (m, 2 H, H_2-2), 3.11 (dt, 1 H, $J_{2,3}$ 7.0, $J_{3,4}$ 3.4 Hz, H-3), 4.08 (dd, 1 H, $J_{8,9b}$ 3.4 $J_{9,9'}$ 12.3 Hz, H-9b), 4.29 (t, 1 H, $J_{3,4} = J_{4,5}$ 3.4 Hz, H-4), 4.34 (m, 1 H, H-8), 4.59 (dd, 1 H, $J_{8,9a}$ 7.7, $J_{9a,9b}$ 12.3 Hz, H-9), 4.88 (t, 1 H, $J_{6,7} = J_{7,8}$ 4.7 Hz, H-7), 5.05 (t, 1 H, $J_{4,5} = J_{5,6}$ 3.4 Hz, H-5), and 5.19 (dd, 1 H, $J_{5,6}$ 3.4, $J_{6,7}$ 4.7 Hz, H-6).

Anal. Calc. for $C_{18}H_{22}N_2O_9$: C, 52.68; H, 5.40; N, 6.83. Found: C, 52.62; H, 5.32; N, 6.69.

Minor isomer. Colorless crystals (from ether), m.p. 134–135°, $[\alpha]_D^{20}$ +21.9° (*c* 0.48, chloroform); ν_{max}^{KBr} 2260 (C≡N) and 1740 (C=O) cm^{-1}; ^{1}H-n.m.r.: δ 2.09 (s, 3 H, OAc), 2.12 (s, 3 H, OAc), 2.15 (s, 3 H, OAc), 2.18 (s, 3 H, OAc), 2.87 (m, 2 H, H_2-2), 3.30 (ddd, 1 H, $J_{2,3}$ 5.4, $J_{2b,3}$ 6.5, $J_{3,4}$ 10.1 Hz, H-3), 4.07 (m, 2 H, H-8,9b), 4.36 (dd, 1 H, $J_{3,4}$ 10.1, $J_{4,5}$ 3.1 Hz, H-4), 4.52 (dd, 1 H, $J_{8,9a}$ 8.6, $J_{9a,9b}$ 13.0 Hz, H-9a), 4.86 (t, 1 H, $J_{6,7} = J_{7,8}$ 4.7 Hz, H-7), 5.08 (dd, 1 H, $J_{4,5}$ 3.1, $J_{5,6}$ 4.7 Hz, H-5), and 5.24 (t, 1 H, $J_{5,6} = J_{6,7}$ 4.7 Hz, H-6).

Anal. Calc. for $C_{18}H_{22}N_2O_9$: C, 52.68; H, 5.40; N, 6.83. Found: C, 52.46; H, 5.37; N, 6.81.

(2RS)-*5,6,7,9-Tetra*-O-*acetyl-4,8-anhydro-2,3-dideoxy-2-methyl*-D-glycero-D-ido-*nonononitrile* (**15**). — To a solution of **7** (2.4 mmol, 1.0 g) and methacrylonitrile (48.7 mmol, 3.3 g) in boiling oxolane (40 mL) were added slowly, under N_2 and irradiation with a high-pressure mercury lamp, a solution of tributyltin hydride (2.9 mmol, 850 mg) in oxolane (30 mL). After 1 h, the solution was evaporated *in vacuo*, the residue dissolved in ether (100 mL), and the solution treated with KF (4.0 g) in water (3 mL). After filtration and column chromatography on silica gel (ether), a mixture of isomers (**15**; 620 mg, 64%) was isolated as crystals in a 61:39 ratio (^{1}H-n.m.r.). The isomers could not be separated and were analyzed as a mixture.

Major isomer. ^{1}H-n.m.r.: δ 1.41 (d, 3 H, J_{2,CH_3} 5.8 Hz, CH_3), 1.62–1.84 (m, 1 H, H-3a), 2.05 (s, 3 H, OAc), 2.06 (s, 3 H, OAc), 2.10 (s, 3 H, OAc), 2.11 (s, 3 H, OAc), 2.20–2.34 (m, 1 H, H-3b), 2.80–2.90 (m, 1 H, H-2), 3.87 (ddd, 1 H, $J_{7,8}$ 8.0, $J_{8,9a}$ 5.7, $J_{8,9a}$ 3.5 Hz, H-8), 4.15 (dd, 1 H, $J_{8,9a}$ 3.5, $J_{9a,9b}$ 12.3 Hz, H-9b), 4.24–4.30 (m, 2 H, H-4,9a), 4.98 (t, 1 H, $J_{6,7} = J_{7,8}$ 8.0 Hz, H-7), 5.10 (dd, 1 H, $J_{4,5}$ 5.0, $J_{5,6}$ 8.0 Hz, H-5), and 5.20 (t, 1 H, $J_{5,6} = J_{6,7}$ 8.0 Hz, H-6).

Minor isomer. ^{1}H-n.m.r.: δ 1.39 (d, 3 H, J_{2,CH_3} 6.0 Hz, CH_3), 1.62–1.84 (m, 1 H, H-3a), 2.04 (s, 9 H, 3 OAc), 2.08 (s, 3 H, OAc), 2.20–2.34 (m, 1 H, H-3b), 2.66–2.78 (m, 1 H, H-2), 3.93 (ddd, 1 H, $J_{7,8}$ 8.5, $J_{8,9a}$ 4.8, $J_{8,9a}$ 2.5 Hz, H-8), 4.12 (dd, 1 H, $J_{8,9a}$ 2.5, $J_{9a,9b}$ 12.5 Hz, H-9b), 4.24–4.30 (m, 2 H, H-4,9a), 5.00 (t, 1 H, $J_{6,7} = J_{7,8}$ 8.5 Hz, H-7), 5.08 (dd, 1 H, $J_{4,5}$ 5.7, $J_{5,6}$ 8.5 Hz, H-5), and 5.26 (t, 1 H, $J_{5,6} = J_{6,7}$ 8.5 Hz).

Anal. Calc. for $C_{18}H_{25}NO_9$: C, 54.14; H, 6.27; N, 3.51. Found: C, 53.80; H, 6.51; N, 3.28.

5,6,7,9-Tetra-O-*acetyl-4,8-anhydro-2,3-dideoxy*-D-glycero-D-talo-*nonononitrile* (**17**). — A boiling solution of **16** (ref. 11; 12.0 mmol, 4.9 g), acrylonitrile (120 mmol, 6.4 g), and tributyltin hydride (13.7 mmol, 4.0 g) in ether (200 mL) was

irradiated with a mercury high-pressure lamp. After 9 h, the mixture was filtered, further acrylonitrile (56.6 mmol, 3.0 g) and tributyltin hydride (6.9 mmol, 2.0 g) were added to the filtrate which was again irradiated for 15 h. The solution was treated with KF (3.0 g) in water (2 mL), filtered and evaporated. Column chromatography on silica gel (5:1 ether–pentane) of the residue gave **17** (3.1 g, 68%), colorless oil, $[\alpha]_D^{20}$ +20.3° (*c* 4.3, chloroform); ν_{max}^{KBr} 2240 (C≡N) and 1750 (C=O) cm^{-1}; ^{1}H-n.m.r.: δ 1.92–2.04 (m, 1 H, H-3a), 2.04–2.15 (m, 1 H, H-3b), 2.09 (s, 3 H, OAc), 2.10 (s, 3 H, OAc), 2.11 (s, 3 H, OAc), 2.12 (s, 3 H, OAc), 2.49 (t, 2 H, $J_{2,3a} = J_{2,3b}$ 7.3 Hz, H_2-2), 3.97 (ddd, 1 H, $J_{7,8}$ 6.5, $J_{8,9}$ 7.7, $J_{8,9a}$ 3.6 Hz, H-8), 4.04 (ddd, 1 H, $J_{3,4}$ 5.8, $J_{3b,4}$ 9.5, $J_{4,5}$ 6.1 Hz, H-4), 4.10 (dd, 1 H, $J_{8,9b}$ 3.6, $J_{9a,9b}$ 12.3 Hz, H-9b), 4.58 (dd, 1 H, $J_{8,9a}$ 7.7, $J_{9a,9b}$ 12.3 Hz, H-9a), 5.07 (dd, 1 H, $J_{4,5}$ 6.1, $J_{5,6}$ 3.5 Hz, H-5), 5.08 (dd, 1 H, $J_{6,7}$ 5.1, $J_{7,8}$ 6.5 Hz, H-7), and 5.26 (dd, 1 H, $J_{5,6}$ 3.5, $J_{6,7}$ 5.1 Hz, H-6).

Anal. Calc. for $C_{17}H_{23}NO_9$: C, 52.99; H, 5.97; N, 3.64. Found: C, 52.95; H, 6.16; N, 3.46.

(*3*RS)-*5,6,7,9-Tetra*-O-*acetyl-4,8-anhydro-3-cyano-2,3-dideoxy*-D-glycero-D-talo-*nononononitrile* (**18**). — To a boiling solution of **16** (3.6 mmol, 1.5 g) and fumarodinitrile (36 mmol, 2.8 g) in toluene (80 mL) was added, under N_2 within 2 h, a solution of tributyltin hydride (7.2 mmol, 2.1 g) and azoisobutyronitrile (240 mg) in toluene (20 mL). After further 30 min, the solution was evaporated, the residue dissolved in acetonitrile (300 mL), and the solution extracted three times with pentane (50 mL each). The acetonitrile solution was treated at reflux with charcoal, filtered, and evaporated. Two column chromatographies of the resulting residue on silica gel (5:4 pentane–ethyl acetate) gave a mixture of isomers (**18**; 510 mg, 34%) in a 69:31 ratio, but it could not be concluded from the ^{1}H-n.m.r. spectra which of the isomers was the (*3R*)-cyano or the (*3S*)-cyano-nononononitrile. The isomers could not be separated and were analyzed as a mixture.

Major isomer. ^{1}H-n.m.r.: δ 2.10 (s, 3 H, OAc), 2.12 (s, 3 H, OAc), 2.14 (s, 3 H, OAc), 2.20 (s, 3 H, OAc), 2.86 (m, 2 H, H_2-2), 3.11 (m, 1 H, H-3), 4.05 (dd, 1 H, $J_{8,9b}$ 4.1, $J_{9a,9b}$ 12.2 Hz, H-9b), 4.17 (m, 1 H, H-8), 4.28 (dd, 1 H, $J_{3,4}$ 7.2, $J_{4,5}$ 9.4 Hz, H-4), 4.83 (dd, $J_{8,9a}$ 9.4, $J_{9a,9b}$ 12.2 Hz, H-9a), 4.91 (dd, 1 H, $J_{6,7}$ 3.6, $J_{7,8}$ 1.8 Hz, H-7), 5.16 (dd, 1 H, $J_{4,5}$ 9.4, $J_{5,6}$ 3.6 Hz, H-5), and 5.34 (t, 1 H, $J_{5,6} = J_{6,7}$ 3.6 Hz, H-6).

Minor isomer. ^{1}H-n.m.r.: δ 2.06 (s, 3 H, OAc), 2.12 (s, 3 H, OAc), 2.18 (s, 3 H, OAc), 2.19 (s, 3 H, OAc), 2.86 (m, 2 H, H_2-2), 3.25 (m, 1 H, H-3), 3.94 (dd, 1 H, $J_{8,9a}$ 3.5, $J_{9a,9b}$ 12.4, H-9b), 4.17 (m, 1 H, H-8), 4.23 (dd, 1 H, $J_{3,4}$ 2.4, $J_{4,5}$ 7.4 Hz, H-4), 4.90 (m, 1 H, H-7), 4.95 (dd, 1 H, $J_{8,9}$ 10.0, $J_{9a,9b}$ 12.4 Hz, H-9a), 5.22 (dd, 1 H, $J_{4,5}$ 7.4, $J_{5,6}$ 3.2 Hz, H-5), and 5.47 (t, 1 H, $J_{5,6} = J_{6,7}$ 3.2 Hz, H-6).

Anal. Calc. for $C_{18}H_{22}O_9N_2$: C, 52.68; H, 5.40; N, 6.83. Found: C, 52.48; H, 5.39; N, 6.70.

4-C-*Acetoxymethyl-4,8-anhydro-5,6,7,9-tetra*-O-*benzyl-2,3-dideoxy*-D-glycero-D-ido-*nononononitrile* (**21**). — To a boiling solution of acrylonitrile (27.0 mmol, 1.43 g) in benzene (60 mL) was added, under N_2 within 3 h, a solution of **20** (ref. 8;

0.90 mmol, 575 mg), tributyltin hydride (1.2 mmol, 350 mg), and azoisobutyronitrile (0.96 mmol, 160 mg) in benzene (90 mL). After 1 h, the solution was evaporated, the residue dissolved in acetonitrile (50 mL), and the solution extracted three times with pentane (30 mL each). The acetonitrile solution was evaporated and the residue chromatographed on silica gel (3:1 hexane–ethyl acetate) to give **21** (274 mg, 47%) after crystallization from ethanol, m.p. 103–105°, $[\alpha]_D^{20}$ +22.4° (*c* 1.2, dichloromethane); ^{1}H-n.m.r.: δ 1.97 (s, 3 H, OAc), 2.10–2.36 (m, 2 H, H_2-3), 2.38–2.48 (m, 2 H, H_2-2), 3.55–3.68 (m, 4 H, H-7,8,9a,9b), 3.73 (d, 1 H, $J_{5,6}$ 9.5 Hz, H-5), 3.85 (dd, 1 H, $J_{5,6}$ 9.5, $J_{6,7}$ 8.5 Hz, H-6), 4.20 (d, 1 H, *J* 11.7 Hz, CH_2OAc), 4.50–4.65 (m, 4 H, 2 benzylic CH_2), 4.86–4.98 (m, 4 H, 2 benzylic CH_2), and 7.20–7.40 (m, 20 H, 4 OBn).

Anal. Calc. for $C_{40}H_{43}NO_7$: C, 73.92; H, 6.67; N, 2.15. Found: C, 73.57; H, 6.74; N, 2.27.

X-Ray crystallographic determination of the structure of **21**. — Space group $P3_2$; *a* 24.083(3), *c* 5.409(1) Å, *V* 2716.9 Å^3, *z* = 3, $D_{calc.}$ 1.191 g·cm^{-1}, and $\mu_{CuK\alpha}$ 5.77 cm^{-1}.

Data collection. A needle (0.15·0.08·2.4 mm) was mounted along *c* on a STE SIADI 4 diffractometer using graphite, monochromated CuKα radiation. The cell constants were determined by measuring the positions of 33 reflections with $15.3 < 2\vartheta < 50.3°$. From 3009 measured reflections ($3 < 2\vartheta < 120°$), 2579 with $F_0 \geqq 3\,\sigma(F_0)'$ were used for structure determination and refinement after correction for background and geometrical factors.

Structure determination and refinement. The structure was solved by use of the MULTAN 80[12] and difference-density syntheses. The hydrogen atoms were placed in calculated positions, 1.08 Å away from their respective carbon atoms (*U* 0.18 Å^2). Anisotropic refinement of the non-hydrogen atoms led[13] to *R* 0.058. The positional parameters and U_{eq} for the non-hydrogen atoms are presented in Table I.

*5,6,7-Tri-*O*-acetyl-4,8-anhydro-2,3-dideoxy-*D*-gulo-octononitrile* (**25**) *and* (*4*RS)*-7,8,9-tri-*O*-acetyl-6,10-anhydro-4-cyano-2,3,4,5-tetradeoxy-*D*-gulo-decanonitrile* (**26**). — To a boiling solution of **24** (ref. 74; 2.95 mmol, 1.0 g) and acrylonitrile (29.5 mmol, 1.6 g) in toluene (50 mL) was added, under N_2, a solution of tributyltin hydride (6.0 mmol, 1.75 g) and azoisobutyronitrile (150 mg) in toluene (30 mL). After 2 h, the solution was evaporated, the residue dissolved in acetonitrile (50 mL), and the solution extracted three times with pentane (30 mL each). The acetonitrile solution was evaporated and the residue chromatographed on silica gel (diethyl ether) to give the 1:1 adduct **25** (301 mg, 33%) and the 2:1 adduct **26** (283 mg, 26%).

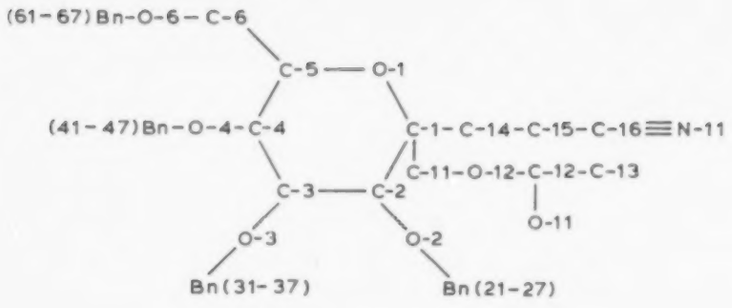
Compound **25**. Colorless crystals, m.p. 94–95° (ether), $[\alpha]_D^{20}$ −36.9° (*c* 0.5, chloroform); ν_{max}^{KBr} 2250 (C≡N) and 1740 (C=O) cm^{-1}; ^{1}H-n.m.r.: δ 1.70–1.78 (m, 1 H, H-3b), 1.84–1.93 (m, 1 H, H-3a), 2.03 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), 2.06 (s, 3 H, OAc), 2.52 (dd, 2 H, $J_{2,3a}$ 6.3, $J_{2,3a}$ 8.2 Hz, H_2-2), 3.29 (t, 1 H, $J_{7,8a} = J_{8a,8b}$ 10.8 Hz, H-8a), 3.46 (dt, 1 H, $J_{3a,4} = J_{4,5}$ 9.6, $J_{3a,4}$ 2.8 Hz, H-4), 4.81 (t, 1 H, $J_{4,5} = J_{5,6}$ 9.6 Hz, H-5), 4.96 (ddd, 1 H, $J_{6,7}$ 9.6, $J_{7,8}$ 5.6, $J_{7,8a}$ 5.6, $J_{7,8b}$ 10.8 Hz, H-7), and

TABLE I

FINAL ATOMIC COORDINATES AND THERMAL PARAMETERS FOR COMPOUND[a] **21**

Atom	x/*A*	y/*B*	z/*C*	U(eq)
C-1	0.0203(3)	−0.7176(3)	0.0619(10)	0.063(3)
C-2	−0.0481(2)	−0.7383(2)	−0.0220(0)	0.056(3)
C-3	−0.0534(2)	−0.6831(2)	−0.1378(10)	0.060(3)
C-4	−0.0220(3)	−0.6226(3)	0.0197(11)	0.065(3)
C-5	0.0447(3)	−0.6078(2)	0.0975(12)	0.069(3)
C-6	0.0717(3)	−0.5534(3)	0.2934(13)	0.088(4)
C-11	0.0225(3)	−0.7654(3)	0.2443(11)	0.073(3)
C-12	0.0243(4)	−0.8619(3)	0.2223(15)	0.098(5)
C-13	0.0076(5)	−0.9193(4)	0.0701(18)	0.160(7)
C-14	0.0655(3)	−0.7049(3)	−0.1569(11)	0.065(3)
C-15	0.1363(3)	−0.6734(4)	−0.0815(13)	0.086(4)
C-16	0.1756(3)	−0.6606(4)	−0.2994(16)	0.089(4)
C-21	−0.1269(3)	−0.8457(3)	−0.1138(13)	0.080(4)
C-22	−0.1552(3)	−0.8927(3)	−0.3266(13)	0.072(4)
C-23	−0.2080(4)	−0.8986(5)	−0.4419(18)	0.137(7)
C-24	−0.2357(5)	−0.9425(8)	−0.6288(23)	0.162(9)
C-25	−0.2122(9)	−0.9802(6)	−0.6904(26)	0.160(11)
C-26	−0.1601(10)	−0.9748(7)	−0.5772(28)	0.241(15)
C-27	−0.1308(6)	−0.9290(5)	−0.3983(18)	0.181(9)
C-31	−0.1399(3)	−0.7026(3)	−0.4057(12)	0.083(4)
C-32	−0.2116(3)	−0.7264(3)	−0.4069(12)	0.072(3)
C-33	−0.2496(4)	−0.7646(4)	−0.5918(16)	0.116(6)
C-34	−0.3163(4)	−0.7841(5)	−0.5906(21)	0.125(7)
C-35	−0.3392(4)	−0.7626(5)	−0.4059(23)	0.128(7)
C-36	−0.3019(4)	−0.7263(5)	−0.2268(19)	0.123(6)
C-37	−0.2381(3)	−0.7078(3)	−0.2268(15)	0.097(5)
C-41	−0.0539(3)	−0.5442(3)	−0.0306(14)	0.103(4)
C-42	−0.0369(3)	−0.4846(3)	−0.1744(12)	0.080(4)
C-43	0.0150(3)	−0.4272(3)	−0.1065(14)	0.094(4)
C-44	0.0290(4)	−0.3718(3)	−0.2430(19)	0.112(5)
C-45	−0.0074(5)	−0.3756(5)	−0.4437(19)	0.147(8)
C-46	−0.0609(5)	−0.4341(5)	−0.5068(17)	0.142(7)
C-47	−0.0741(3)	−0.4876(4)	−0.3721(14)	0.100(5)
C-61	0.1656(5)	−0.4857(4)	0.5086(20)	0.154(7)
C-62	0.1813(4)	−0.4244(3)	0.3724(17)	0.095(5)
C-63	0.1546(4)	−0.3885(5)	0.4364(20)	0.133(7)
C-64	0.1682(5)	−0.3328(5)	0.3151(29)	0.165(6)
C-65	0.2059(5)	−0.3159(5)	0.1244(33)	0.174(10)
C-66	0.2370(5)	−0.3474(6)	0.0520(24)	0.152(9)
C-67	0.2235(5)	−0.4039(5)	0.1730(23)	0.135(7)
N-11	0.2052(3)	−0.6509(3)	−0.4752(15)	0.119(5)
O-1	0.0417(2)	−0.6624(2)	0.2184(7)	0.066(2)
O-2	−0.0718(2)	−0.7892(2)	−0.1986(7)	0.058(2)
O-3	−0.1201(2)	−0.7035(2)	−0.1621(7)	0.067(2)
O-4	−0.0163(2)	−0.5700(2)	−0.1199(6)	0.070(2)
O-6	0.1341(2)	−0.5395(2)	0.3463(13)	0.140(4)
O-11	0.0101(2)	−0.8219(2)	0.1114(8)	0.090(3)
O-12	0.0433(3)	−0.8540(3)	0.4319(12)	0.142(4)

[a]For numbering scheme, see **30**.



30

5.19 (t, 1 H, $J_{5,6} = J_{6,7}$ 9.6 Hz, H-6).

Anal. Calc. for $C_{14}H_{19}NO_7$: C, 53.67; H, 6.07; N, 4.47. Found: C, 53.56; H, 6.21; N, 4.51.

Compound **26**. Mixture of diasteromers, only from the ^{1}H-n.m.r. data of the main isomer could all lines be identified; ^{1}H-n.m.r.: δ 1.85–1.95 (m, 2 H, H_2-5), 1.97–2.17 (m, 2 H, H_2-3), 2.03 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), 2.06 (s, 3 H, OAc), 2.52–2.66 (m, 2 H, H_2-2), 2.94–2.99 (m, 1 H, H-4), 3.28 (t, 1 H, $J_{9,10} = J_{10a,10b}$ 9.5 Hz, H-10a), 3.52 (dt, 1 H, $J_{5a,6}$ 3.9, $J_{5b,6} = J_{6,7}$ 9.5 Hz, H-6), 4.14 (dd, 1 H, $J_{9,10b}$ 5.5, $J_{10a,10b}$ 9.5 Hz, H-10b), 4.84 (t, 1 H, $J_{6,7} = J_{7,8}$ 9.5 Hz, H-7), 4.79 (dt, 1 H, $J_{8,9} = J_{9,10b}$ 9.5, $J_{9,10a}$ 5.5 Hz, H-9), and 5.18 (t, 1 H, $J_{7,8} = J_{8,9}$ 9.5 Hz, H-8).

Anal. Calc. for $C_{17}H_{22}N_2O_7$ (mixture): C, 55.73; H, 6.05; N, 7.65. Found: C, 55.91; H, 5.81; N, 7.41.

*5,6,7-Tri-*O*-acetyl-4,8-anhydro-2,3-dideoxy-*D*-talo-octononitrile* (**28**) *and 5,6,7-tri-*O*-acetyl-4,8-anhydro-2,3-dideoxy-*D*-galacto-octononitrile* (**29**). — To a boiling solution of **27** (ref. 15, 5.9 mmol, 2.0 g) and acrylonitrile (59.0 mmol, 3.0 g) in toluene (60 mL) was added, under N_2, a solution of tributyltin hydride (9.0 mmol, 2.55 g) and azoisobutyronitrile (200 mg) in toluene (40 mL). After 3 h, the solution was evaporated, the residue dissolved in acetonitrile (50 mL), and the solution extracted three times with pentane (50 mL each). The acetonitrile solution was evaporated and the residue chromatographed on silica gel (diethyl ether) to give **28** (870 mg, 47%) and **29** (401 mg, 21%) as colorless oils.

Compounds **28**. $[\alpha]_D^{20}$ −13.6° (*c* 4.2, chloroform); ν_{max}^{KBr} 2250 (C≡N) and 1745 (C=O) cm^{-1}; ^{1}H-n.m.r.: δ 1.99–2.02 (m, 1 H, H-3b), 2.02 (s, 3 H, OAc), 2.10–2.20 (m, 1 H, H-3a), 2.15 (s, 6 H, OAc), 2.50–2.56 (m, 2 H, H_2-2), 3.77 (dt, 1 H, $J_{3a,4}$ 2.6, $J_{3a,4} = J_{4,5}$ 9.9 Hz, H-4), 3.82–3.95 (m, 2 H, H_2-8), 4.84 (dt, 1 H, $J_{6,7} = J_{7,8}$ 9.0, $J_{7,8}$ 1.8 Hz, H-7), 4.92 (dd, 1 H, $J_{4,5}$ 9.9, $J_{5,6}$ 9.0 Hz, H-5), and 5.34 (t, 1 H, $J_{5,6} = J_{6,7}$ 9.0 Hz, H-6).

Anal. Calc. for $C_{14}H_{19}NO_7$: C, 53.67; H, 6.07; N, 4.47. Found: C, 53.41; H, 5.98; N, 4.21.

Compounds **28**. $[\alpha]_D^{20}$ −39.5° (*c* 2.2, chloroform); ν_{max}^{KBr} 2260 (C≡N) and 1745 (C=O) cm^{-1}; ^{1}H-n.m.r.: δ 1.60–1.80 (m, 1 H, H-3a), 1.80–2.00 (m, 1 H, H-3b), 2.01 (s, 3 H, OAc), 2.05 (s, 3 H, OAc), 2.17 (s, 3 H, OAc), 2.46–2.56 (m, 2 H, H_2-2), 3.29 (dd, 1 H, $J_{7,8a}$ 10.3, $J_{8a,8b}$ 11.2 Hz, H-8a), 3.69 (ddd, 1 H, $J_{3a,4}$ 3.4, $J_{3b,4}$ 10.0,

$J_{4,5}$ 1.1 Hz, H-4), 4.17 (dd, 1 H, $J_{7,8b}$ 5.5, $J_{8a,8b}$ 11.2 Hz, H-8b), 5.06 (dd, 1 H, $J_{5,6}$ 3.4, $J_{6,7}$ 10.3 Hz, H-6), 5.20 (dt, 1 H, $J_{6,7} = J_{7,8a}$ 10.3, $J_{7,8a}$ 5.5 Hz, H-7), and 5.34 (dd, 1 H, $J_{4,5}$ 1.1, $J_{5,6}$ 3.4 Hz, H-5).

Anal. Calc. for $C_{14}H_{19}NO_7$: C, 53.67; H, 6.07; N, 4.47. Found: C, 53.61; H, 6.12; N, 4.35.

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Note

Stereoselectivity in the formation of pentacarbonyl glycosylmanganese complexes*

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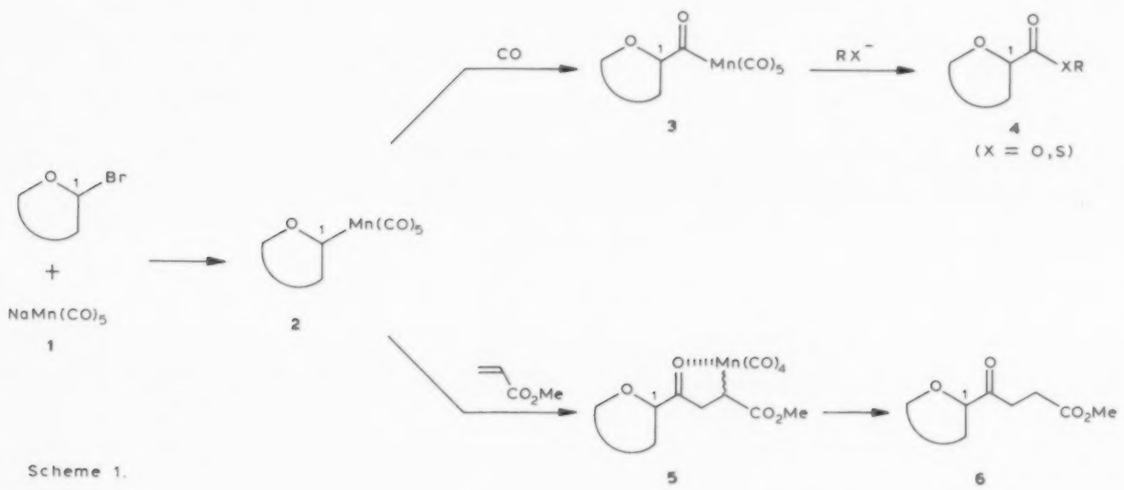
We have recently reported[1] an approach to the synthesis of C-glycosyl compounds in which stable pentacarbonylglycosylmanganese complexes (**2**) were prepared by condensation of the corresponding glycosyl bromide with sodium pentacarbonylmanganate(I) (**1**), and the resulting pentacarbonylmanganese complexes were induced to undergo migratory insertion to give the acylmanganese complex **3**. Cleavage of the acylmanganese complex with alkoxide or thiolate (Reppe reaction) then produced the ester derivatives **4**. Alternatively, the manganese complex **2** underwent high pressure-induced sequential insertion of carbon monoxide and methyl acrylate to furnish the manganacycle **5**. Subsequent photodemetalation of **5** resulted in formation of the *C*-glycosyl compound **6** (see Scheme 1).

For this approach to have maximum versatility as a method of synthesizing *C*-glycosyl compounds, the condensation reaction which furnishes the penta-



Scheme 1.

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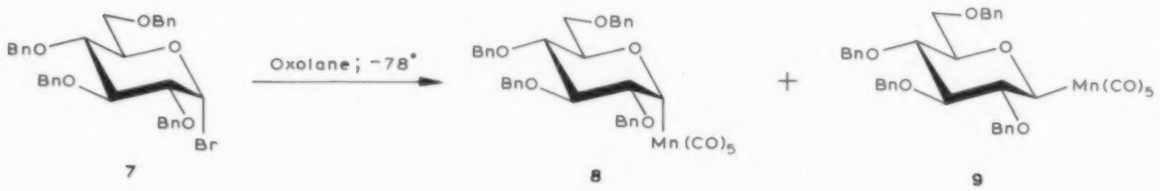
TABLE I

REACTION OF COMPOUND **1** WITH COMPOUND **7**

Conditions	*Yield (%)*	*Ratio* **8** *to* **9**
$NaMn(CO)_5$	75	0:100
$NaMn(CO)_5$, 3 equiv. $Bu_4N^+Br^-$	50	3:2
$NaMn(CO)_5$, 3 equiv. KBr	90	0:100



7 8 9

carbonylglycosylmanganese complex **2** must be highly stereoselective since the stereochemistry at C-1 of complex **2** defines the stereochemistry of the *C*-glycosyl compounds **4** and **6**, respectively. That is, the glycosyl complex **2** carrying the β-D configuration at C-1 is transformed into the *C*-glycosyl compounds **4** and **6** in which the new carbon–carbon bond has been produced with retention of the β-D configuration[2].

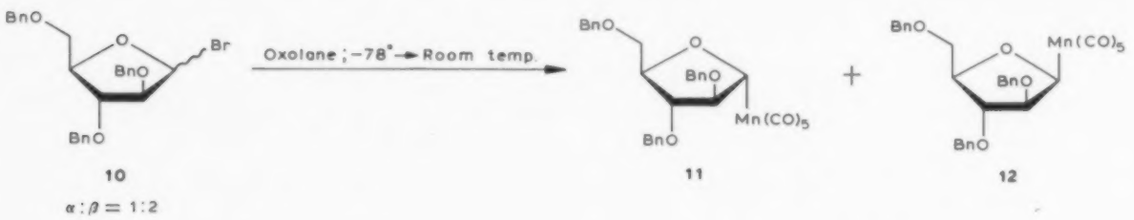
We report herein, that the stereoselectivity and the yield of the condensation of sodium pentacarbonylmanganate(I) (**1**) with D-glucopyranosyl and D-arabinofuranosyl bromides can be influenced by the addition of bromide salts to the condensation reaction mixture. Reaction of sodium pentacarbonylmanganate(I)[6] (**1**) with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromides[3] (**7**) in oxolane at −78° gave the β-manganese complex **9** *stereospecifically* in 75% yield (Table I)[1]. In this instance, the condensation appeared to proceed in an SN2 fashion with strict inversion of configuration at C-1.

Introduction of tetrabutylammonium bromide (Bu_4NBr) to the reaction mixture of **1** and bromide **7** had a pronounced effect upon the stereoselectivity of the condensation. When three equivalents of Bu_4NBr were suspended in the reaction mixture at −78°, a 3:2 mixture of glucosyl complexes **8** and **9** was obtained in 50% yield. Addition of Bu_4NBr had (a) caused a significant decrease in the yield of product and more importantly, (b) had caused a decline in the stereoselectivity of the condensation. α-Complex **8**, which had not been detected in the reaction of **1** and **7** in the absence of excess bromide, became the preponderant product in the presence of Bu_4NBr (Table I). We also demonstrated that the cation of the salt had an influence upon the condensation. Replacement of Bu_4NBr with potassium bromide dramatically improved the yield of manganese complex from 75 to 90% However, the stereoselectivity was not altered by the presence of KBr; only the β-complex **9** was obtained.

TABLE II

REACTION OF COMPOUND **1** WITH COMPOUND **10**

Conditions	*Yield (%)*	*Ratio* **11** *to* **12**
$NaMn(CO)_5$	70	2:1
$NaMn(CO)_5$, 3 equiv. $Bu_4N^+Br^-$	55	>98:2
$NaMn(CO)_5$, 3 equiv. KBr	90	2:1



10
$\alpha:\beta = 1:2$

11 **12**

An analogous trend of results was observed in the furanosyl sugar series as outlined in Table II. Treatment of a 1:2 mixture of 2,3,5-tri-*O*-benzyl-α- and -β-D-arabinofuranosyl bromide (**10**) with sodium pentacarbonylmanganate(I) produced the manganese complexes **11** and **12** in a 2:1 ratio. As described above, the condensation proceeded with inversion of configuration at C-1 in the absence of excess bromide salts. Introduction of three equivalents of Bu_4NBr into the reaction mixture had a deleterious effect upon the yield of **11** and **12**, as was observed in the pyranosyl series. However, the stereoselectivity of the condensation was significantly enhanced, and only a trace of β-complex **12** could be detected in the crude reaction mixture. The presence of excess KBr in the reaction mixture of **1** and **10** again led to an improvement in the overall yield of complexes **11** and **12** (90% *vs.* 70%) in the absence of KBr, but the stereoselectivity of the condensation remained unchanged.

We propose that the results summarized in Tables I and II demonstrate that the stereoselectivity in the reaction of sodium pentacarbonylmanganate (**1**) and glycosyl bromides was influenced in two fashions by the presence of Bu_4NBr or KBr. The first involved a cation effect[4]. Addition of excess tetrabutylammonium or potassium salts to **1** led to cation exchange with sodium and formation of tetrabutylammonium and potassium manganate, respectively. This proposal of a cation effect is supported by the qualitative observation that the relative rates of condensation under the three sets of reaction conditions differed as indicated: **1** + KBr > **1** > **1** + Bu_4NBr. The observed trend in the relative rates also was reflected in the yields of adducts formed under the respective conditions. The set of reaction conditions that gave the fastest rate (**1** + KBr) also gave the highest yield of product. This suggested that the decreased yield of adducts obtained from the other sets of conditions may be the result of decomposition of glycosyl bromides **7** and **10**,

respectively, under the prolonged reaction times required for consumption of the unstable glycosyl bromides.

Alteration of the condensation stereoselectivity can also be rationalized by the cation effect. The rate of displacement of bromide from glycosyl bromides **7** and **10** was fast with either **1** or **1**–KBr, and the reaction proceeded with inversion of configuration at C-1. However, in the presence of Bu_4NBr, the rate of condensation decreased to the point that the rate of bromide ion-induced anomerization of **7** and **10** became competitive with the condensation[5]. Therefore, the anomeric ratios of **7** and **10** changed during the course of the SN2 displacement by manganate anion and resulted in alteration of the stereoselectivity (see Tables I and II).

The results reported herein indicate that the nucleophilic displacement of glycosyl halides by manganate anion can be influenced by reaction parameters, and we have begun a systematic investigation into this topic.

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